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# Combined oral estradiol valerate–norethisterone treatment over three years in postmenopausal women. 1. Clinical aspects and endometrial histology

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## ABSTRACT

*The aim of this study was to determine the medium-term safety and efficacy of once-daily, oral estradiol valerate 2 mg with norethisterone 0.7 mg on menopausal symptoms, bleeding incidence, endometrial pathology, adverse events and other clinical parameters. A three-year, single-center, open study was performed. Women with menopausal symptoms and ≥ 6 months since the last spontaneous menstrual period were recruited. Patients were assessed using questionnaires and daily records of bleeding incidence and severity. Adverse events were recorded at each visit and endometrial histopathology was determined at baseline and annually.*

*There were 206 patients at entry and 133 completers at the end of year 3. Menopausal symptoms showed significant improvements within 4 months ($p < 0.0001$ compared with baseline). By the end of month 4, 79.9% of patients had stopped bleeding. The mean number of days bleeding per month declined from 2.8 (month 1) to 1.1 (month 12). Significantly less bleeding was observed in patients who were ≥ 2 years postmenopausal. No abnormalities in endometrial histology were found. Bleeding and breast tenderness were the commonest adverse events. Twenty-four patients experienced serious adverse events although no definite relationship to drug therapy was considered likely. We therefore conclude that the oral combination of estradiol valerate 2 mg and norethisterone 0.7 mg given daily and con- tinuously leads to amenorrhea and symptom alleviation in the majority of patients and is well tolerated.*

## INTRODUCTION

One reason for poor uptake or non-compliance with oral regimens of hormone replacement therapy (HRT) in postmenopausal women is the presence of monthly (or 3-monthly) withdrawal bleeds. Although bleeding with sequential HRT preparations is generally regular, the majority of postmenopausal women prefer to be amenorrheic[1,2] and still have the benefits of HRT. Combined continuous preparations recently introduced (Premique®, Wyeth Laboratories, Maidenhead, UK; Kliofem®, Novo Nordisk Pharmaceuticals, Crawley, UK) have addressed this

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problem but the lowest safe doses of combined estrogens and progestogens compatible with efficacy are still not known.

We examined the effect of a combination of estradiol valerate and norethisterone given as a combined tablet continuously without any break in therapy (Climesse®/Merigest®, Sandoz, Camberley, UK). Estradiol valerate in a dose of 2 mg daily was chosen because it is effective in the control of menopausal symptoms with minimal effect on liver function, and is effective in the prevention and treatment of osteoporosis. Estradiol valerate was combined with norethisterone since it is an effective and well-known progestogen. It has been established that estrogens have beneficial effects on serum lipids which are reversed by some progestogens, but the beneficial effects and the reversal are both dose-dependent[3–5]. Norethisterone 0.7 mg daily was chosen as being the dose causing minimal effect, if any, on serum lipids while preventing estrogen-stimulated proliferation of the endometrium[6–10].

This paper reports on the effects of Climesse on menopausal symptoms, bleeding pattern, endometrial histopathology, adverse events, and their interrelationships. Results of lipid levels, hematological parameters, coagulation factors and effect on bone mineral density will be reported separately.

## METHODS

### Patients

A total of 243 postmenopausal women who had not received HRT within the last 3 months and who currently had symptoms requiring therapy were recruited to this single-center study. Postmenopause was defined as more than 6 months since the last spontaneous menstrual period. Those who had stopped HRT between 3 and 6 months previously were required to have a clear history of menopausal symptoms. Patients were excluded who had a current serious medical illness, undiagnosed vaginal bleeding, previous hysterectomy, malignant disease or a history of thromboembolism. Concomitant medication was recorded throughout the study.

### Study design

This was an open-label study. No control group was envisaged since the long duration of the study and the known efficacy of HRT made a placebo group unwarranted and not germane to our objective of determining endometrial safety and efficacy with this particular combination. Patients received one tablet a day of estradiol valerate 2 mg in a fixed combination with norethisterone 0.7 mg. All patients gave written informed consent. The study protocol was approved by the Medical Ethics Committee to the Endocrine Centre and ethical approval to continue the study was obtained for each year of the study.

### Assessments

Patients were clinically examined prior to entry into the study, treated and monitored firstly for 12 months and, for those patients who were eligible, for a further 24 months. The term 'month' refers to a 28-day period of treatment rather than a calendar month. Clinical assessments were carried out during the initial pre-treatment visit (visit 1) and at months 2, 4, 6, 8, 12, 18, 24, 30 and 36 (visits 2, 3, 4, 5, 6, 7, 8, 9 and 10, respectively). Weight and blood pressure were recorded at all visits. Additional investigations, bilateral mammography, dilatation and curettage (D + C) and hysteroscopy, were performed if clinically indicated. Adverse and serious events were recorded in a standard manner at each visit.

### Menopausal symptoms

These were recorded at every visit through completion of a symptom questionnaire to determine the number of hot flushes in the previous week; a visual analog scale was included for all other symptoms, graded 0–100%.

### Bleeding pattern

Patients were supplied with a diary card in which to make daily records of bleeding (0 = none) and its severity according to a rating scale (1 = spotting, 2 = light, 3 = moderate, 4 = heavy).

### Endometrial biopsy

Endometrial specimens were taken pre-treatment and at years 1, 2 and 3 using the Pipelle technique. Classification was assigned to two independent

pathologists unaware of the pre- or post-treatment status of the patient and who issued a final report according to established and agreed criteria[11].

## Adverse events

All adverse events were recorded at each visit on a patient record form. Patients were prompted to report any adverse events by being asked if they had had any symptoms since the previous visit. The investigator then recorded the event, date of onset, severity, duration, course and investigator's opinion on relationship to the trial drug on a special adverse events sheet.

## Statistical analyses

For a comparison of demographic characteristics between completers and non-completers, unpaired *t* tests and Wilcoxon rank sum tests were performed. For the evaluation of changes versus baseline, paired *t* tests and the Wilcoxon matched-pairs signed-ranks tests were applied. In addition, for certain parameters, 95% confidence intervals were calculated.

# RESULTS

Two hundred and six of the 243 patients recruited entered the study by commencing treatment. Thirty-seven patients did not receive treatment owing to failure to meet exclusion/inclusion criteria during the initial screening.

Table 1 lists the demographic data regarding age, height, weight and time since the menopause for all patients entering the study, and at the end of year 1 separately for completers and non-completers; there were no significant differences. The numbers of non-completers in years 2 and 3 were too small to permit meaningful comparisons with other subgroups.

At the end of year 1, 80% of the patients (164/206) had completed the trial as per protocol. There were 40 non-completers and two ineligible patients. In year 2, 70% (144/206) completed, 12 did not enter and 8 were non-completers. In year 3, 65% (133/206) completed, 5 did not enter and six were non-completers.

## Weight

There was no statistically significant difference in mean weight between pre-treatment and the end of year 1 (Table 1). Pre-treatment mean weight (± SD) for those who completed year 2 ($n = 144$) was $66.3 \pm 10.5$ kg compared with $66.5 \pm 11.0$ kg ($p = 0.73$) at the end of year 2. Similarly, for year 3 ($n = 133$), pre-treatment mean weight was $65.6 \pm 10.1$ kg compared with $66.5 \pm 10.1$ kg ($p = 0.0124$).

**Table 1** Patient demographic data

| *Demographic variables* | *Total number of patients* ($n = 206$) | *Completers year 1* ($n = 164$) | *Non-completers year 1* ($n = 42$) |
|---|---|---|---|
| Age (years) | | | |
| range | 41.0–86.0 | 41.0–72.0 | 47.0–86.0 |
| mean | 55.7 | 55.6 | 56.2 |
| SD | 6.2 | 6.2 | 6.5 |
| Height (cm) | | | |
| range | 147.5–177.0 | 147.5–175.0 | 148.0–177.0 |
| mean | 161.5 | 161.6 | 161.5 |
| SD | 5.9 | 5.7 | 6.7 |
| Weight (kg) | | | |
| range | 33.0–136.0 | 41.8–136.0 | 33.0–99.8 |
| mean | 67.0 | 66.9 | 67.4 |
| SD | 12.7 | 11.9 | 15.8 |
| Time since menopause (months) | | | |
| range | 7.0–360.0 | 7.0–360.0 | 8.0–312.0 |
| mean | 76.4 | 73.9 | 86.8 |
| SD | 65.9 | 64.0 | 73.1 |

## Blood pressure

Mean systolic blood pressure changed slightly during the study, with a decrease followed by a return to levels similar to pre-treatment. However, the changes were not significantly different at the end of year 3 from pre-treatment.

Mean diastolic blood pressure declined slightly but significantly from 84.9 mmHg at visit 1 to 80.7 mmHg ($p < 0.0001$) and 81.6 mmHg ($p < 0.002$) at the end of years 1 and 3, respectively. These results are consistent with most HRT studies, which have not shown an adverse effect on blood pressure[12,13].

Two patients were reported as having hypertension. One patient, with hypertension for ten years before starting the study and on treatment with amiloride, was found to have a blood pressure of 130/90 mmHg and was discontinued at her request. A second patient was reported as having 'mild hypertension which worsened' even though pre-treatment examination showed a blood pressure of 150/100 mmHg and the same at visit 2.

## Menopausal symptoms

Menopausal symptoms evaluated were hot flushes, sweating, vaginal dryness and a number of quality-of-life parameters. Symptoms in completers and non-completers were similar, both pre-treatment and during therapy. The similarity of mean pre-treatment results between completers and non-completers in year 1 indicates that the number and type of symptoms experienced pre-treatment are not a predictor for completion. Similarly, the closeness of results for completers and non-completers during year 1 suggests that (for the group but not necessarily for individual patients) the continuation of menopausal symptoms during therapy was not in general a reason for discontinuation.

### *Hot flushes*

Hot flushes per day showed a marked and significant reduction from a pre-treatment mean of 2.1 flushes per day to 0.04 per day at the end of year 1 ($p < 0.0001$) and to 0.03 per day for both years 2 and 3 (both $p < 0.0001$). The majority of the improvement, to a mean of 0.06 flushes per day ($p < 0.0001$), occurred within the first 4 months. These results are illustrated in Figure 1.

Pre-treatment, 82 of 164 patients complained of flushes; by the end of year 1 this was reduced to 5 of 163 patients (no data on one patient), to 3 of 144 patients by the end of year two, and to 3 of 133 patients who completed the study.

### *Sweating*

This was much improved during treatment from a baseline of 47.1% (SD 54.6%) (where 0% equalled 'none at all' and 100% was 'a great deal') to a mean of 9.8% within the first 2 months ($p < 0.0001$), where it remained for the rest of the study. These results are shown in Figure 2.

Ninety-nine of 163 patients (60.7%) (one patient no data) had sweating attacks of more than 10% at the start of the study. However, 31 of the 163 patients had no complaints of sweating during

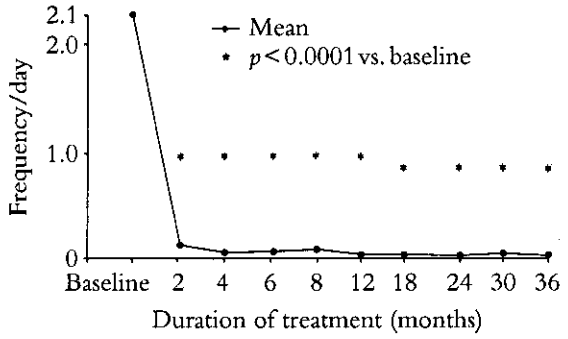


**Figure 1** Number of flushes per day among patients ($n \leq 164$) treated with estradiol valerate (2 mg) and norethisterone (0.7 mg) once daily for up to three years

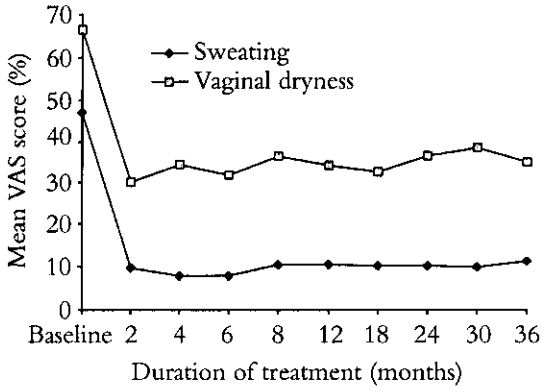


**Figure 2** Frequency and/or degree of sweating and vaginal dryness among patients ($n \leq 164$) treated with estradiol valerate (2 mg) and norethisterone (0.7 mg) once daily for up to three years. Sweating: 0%, none; 100%, a great deal. Vaginal dryness: 0%, not dry (moist); 100%, very dry

the previous week and another 33 had sweating which measured 10% or less on the scale. By the end of years 1, 2 and 3, there were 31, 30 and 31 patients, respectively, (approximately 19%) who complained of sweating attacks that measured more than 10%, and the great majority of patients had no attacks at all. The difference from baseline to all other visits was significant ($p < 0.0001$). Subsequent visits did not differ significantly from each other, thus the effect of Climesse on sweating attacks appeared to occur entirely within the first 2 months of therapy.

### *Vaginal dryness*

Vaginal dryness (0% = moist and 100% = dry) was improved in the previous 7 days in the majority of patients from a pre-treatment mean of 66.4% (SD 24.9%) to an average for all other visits in the region of 30–36% (with SD of approximately 20%). The difference between pre-treatment visit and all other visits was significant ($p < 0.0001$). These results are shown in Figure 2.

### *Tenseness and irritability*

Tenseness and irritability (where 100% was a great deal of irritability and tenseness and 0% was none at all) were much improved with a group mean which declined from a pre-treatment value of 52.4% to 27.3% at month 2 and 26.1% at year 1. The differences between pre-treatment level and all subsequent visits were significant ($p < 0.0001$). Subsequent visits did not differ significantly from each other, thus the effect of Climesse on tenseness and irritability appears to occur entirely within the first 2 months of therapy.

### *Depression*

Depression (where 0% = none at all and 100% = very depressed) was variable in many patients, as was to be expected. In some cases there appeared to be a rapid beneficial effect, with a strong trend towards continued improvement during the course of the study. The group mean showed a definite and clinically important improvement, from a pre-treatment mean of 40.2% to between 22.0% and 27.0% at subsequent visits ($p < 0.0001$).

### *Libido*

Libido, which was defined as interest in sex in the preceding 7 days (where 0% = none at all, and 100% = a great deal) was clinically slightly improved for the group during the course of therapy, from a pre-treatment mean of 27.9% to a mean of 39.3% at the end of year 1. The mean value for month 2 did not differ significantly from pre-treatment ($p = 0.20$); subsequent visits were significantly different from pre-treatment and month 2 ($p \leq 0.0001$). It would appear therefore that improvement in libido for the group mean does not occur until month 4 and either no further improvement or only minimal improvement takes place thereafter.

### *Ability to cope*

The 'ability to cope' (where 0% = less well and 100% = better) with life over the 7 days prior to the clinic visit, as compared to previously, varied widely in many patients, although the group mean showed improvement from a pre-treatment value of 56.2% to values between 63.4% and 68.4% at subsequent visits. The group differences between pre-treatment and values at all other visits were significant ($p < 0.0001$).

## Bleeding pattern

All patients had amenorrhea prior to the start of the study. However, many patients had bleeding in the first few months of therapy. This may have been related to the start of hormone therapy, but may also have been due to the endometrial sampling at entry to the study since further bleeding occurred at or just after endometrial sampling points later in the study.

### *Days of bleeding*

These varied widely between patients. The mean number of days bleeding per patient per month are shown in Table 2. During month 1 of treatment there was a mean of 2.8 days bleeding, increasing during months 2 and 3 to 4.0 and 3.3, respectively, but decreasing from month 4 onwards. The reductions from month 4 (compared to month 1) were statistically significant, (at least $p = < 0.05$, and mostly $p = 0.0001$). By months 11 and 12

mean bleeding was 1.1 days per month ($p = 0.0001$).

### *Amenorrhea*

During the first 12 months of therapy 28% of patients (47/164) who completed year 1 did not bleed at all; 45% (65/144) completing year 2 and 59% (79/133) completing year 3 did not bleed during the second and third 12 months, respectively.

The time to onset of amenorrhea (i.e. total absence of any bleeding or spotting) for the first 12 cycles of therapy is shown in Table 3. By month 5, 56.7% of patients had amenorrhea and did not bleed again, and by month 9 this reached 73.2% of patients.

During year 2, 45.1% (65/144) of patients had total amenorrhea and a further 38 patients (26.4%) had bleeding for 9 days or less in the 12 months.

### *Long-term bleeding*

Patients with long-term bleeding were defined as those having bleeding of any grade for at least 1 day in the month for a period of 6 months or more. There were 29, 7 and 8 such patients in years 1, 2 and 3, respectively. Approximately half of these in year 1 had 20 or more days bleeding each month. Nine patients bled > 90 days during year 1, and four bled > 90 days during year 2 of which three were the same patients as in year 1; these three patients continued with long-term bleeding in year 3.

**Table 2** Mean number of days bleeding per patient per month in completers

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Year 1* ($n = 164$) | | | | | | | | | | | | |
| Month | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| Total days | 462 | 654 | 544 | 407 | 295 | 324 | 293 | 236 | 271 | 266 | 186 | 174 |
| Mean | 2.8 | 4.0 | 3.3 | 2.5 | 1.8 | 2.0 | 1.8 | 1.4 | 1.7 | 1.6 | 1.1 | 1.1 |
| *Year 2* ($n = 144$) | | | | | | | | | | | | |
| Month | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
| Total days | 261 | 131 | 131 | 144 | 112 | 114 | 102 | 97 | 145 | 134 | 96 | 164 |
| Mean | 1.81 | 0.91 | 0.91 | 1.00 | 0.78 | 0.79 | 0.71 | 0.67 | 1.00 | 0.93 | 0.67 | 1.14 |
| *Year 3* ($n = 133$) | | | | | | | | | | | | |
| Month | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 |
| Total days | 214 | 87 | 97 | 72 | 69 | 108 | 93 | 64 | 57 | 52 | 72 | 99 |
| Mean | 1.61 | 0.65 | 0.73 | 0.54 | 0.52 | 0.81 | 0.71 | 0.49 | 0.44 | 0.40 | 0.55 | 0.76 |

The term month represents a 28-day period

**Table 3** Amenorrhea in year 1 – time to onset and patient frequency

| *Month* | *Number of patients who developed amenorrhea during month* | *Total number of patients with amenorrhea* | *Total % with amenorrhea* ($n = 164$) |
|---|---|---|---|
| 1 | 47 | 47 | 28.7 |
| 2 | 9 | 56 | 34.1 |
| 3 | 15 | 71 | 43.3 |
| 4 | 14 | 85 | 51.8 |
| 5 | 8 | 93 | 56.7 |
| 6 | 4 | 97 | 59.1 |
| 7 | 11 | 108 | 65.8 |
| 8 | 5 | 113 | 68.9 |
| 9 | 7 | 120 | 73.2 |
| 10 | 6 | 126 | 76.8 |
| 11 | 9 | 135 | 82.3 |
| 12 | 7 | 142 | 86.6 |

The term month represents a 28-day period

### *Moderate or heavy bleeding*

This was recorded by 40, 13 and 8 patients in years 1, 2 and 3, respectively. Such bleeding did not occur every month, the mean number of cycles per patient where moderate or heavy bleeding was recorded being 2.1 in year 1, 2.1 in year 2 and 2.75 in year 3, the latter weighted by one patient with heavy and long-term bleeding.

### *Continuity of bleeding*

Continuity of bleeding was reported by 43 patients who were bleeding at month 4, and 27 of these were bleeding at month 6. Twelve were still bleeding at month 12, and eight of these continued into year 2 with seven still bleeding at the end of year 2.

Examining bleeding by total number of days, there were 20 patients who had a total of 20 or more days bleeding during the first 4 months of year 1 and were still bleeding at month 6. Fifteen continued with prolonged and often severe bleeding for the rest of year 1; of these 11 continued into year 2 and five were still bleeding at month 24.

Some patients had no bleeding, or very little bleeding, during year 1 but were troubled during year 2. Two patients who had 0 and 5 days total bleeding in year 1, had 61 and 131 days, respectively, in year 2.

### *Bleeding and duration since menopause*

It was expected that less bleeding would be observed in patients who were two or more years postmenopausal. Results were analyzed for the first 12 months of therapy and categorized by time since the menopause, as well as by severity. These are illustrated in Figure 3.

During the first year, significantly less bleeding was observed in patients who were more than 2 years postmenopausal (mean 21 days, median 5 days) as compared with patients who were 6–24 months postmenopausal (mean 34, median 15 days) ($p = 0.0049$).

## Endometrial histopathology

The results of endometrial sampling at baseline and at the end of each year of therapy are shown in Table 4. The majority of endometrial specimens prior to, and during, most of therapy were classified as atrophic; a number of patients had biopsies that were categorized as 'insufficient' or 'inactive', which are interpreted as being atrophic.

Endometrial sampling showed no abnormal pattern throughout the 3 years, with no examples of hyperplasia, atypia or carcinoma. Two endometrial samples recorded prior to therapy as proliferative (one 'mid-proliferative' and the other 'disturbed proliferative') were atrophic at the

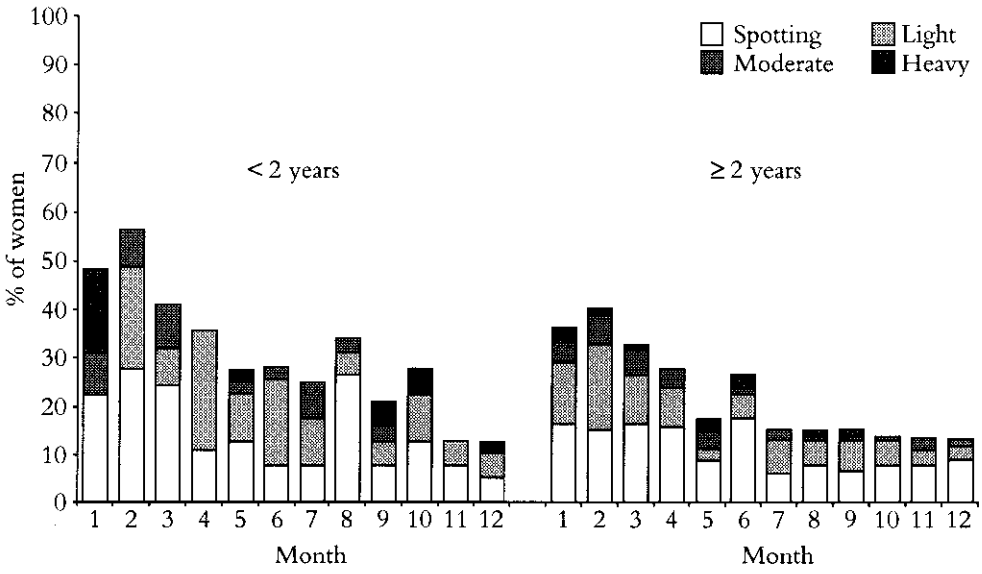


**Figure 3** Severity of bleeding on estradiol valerate/norethisterone in year 1 vs. time since menopause

completion of 12 months' therapy; one patient did not enter year 2, but the other completed year 2 and had an atrophic endometrium at 24 months.

One specimen was proliferative at the end of 12 months' therapy (see Table 4). Prior to treatment, the sample from this patient was atrophic. The patient bled for 18 days during year 1, and had no bleeding during the 2 months prior to endometrial sampling. The patient started treatment 14 months after the menopause, had no symptoms suggestive of hyperestrogenicity and had an estradiol level of 65 pmol/l pre-treatment and 496 pmol/l at the end of year 1. Six months after completion of the 12-month study an endometrial biopsy showed atrophy.

Operative investigation by D + C and hysteroscopy was undertaken during year 1 in 14 patients with heavy or long-term bleeding. Endometrial sample at operation were insufficient in six cases, atrophic in five, secretory in two and no specimen was obtained in one patient who had a normal uterine cavity. There was no evidence of endometrial abnormality in any of these samples.

## Bleeding and endometrial histology

In order to determine if there was any relationship between bleeding pattern and endometrial histology, the endometrial results of two extreme subgroups were compared: those with heavy, prolonged bleeding (i.e. 5 or more months bleeding in the first year, and at least 1 cycle of moderate or heavy bleeding), and those with no bleeding on any day in year 1. The results in Table 5 show that whether there was heavy continuous bleeding, or no bleeding, did not appear to affect the endometrial results.

All those with no bleeding had atrophic, insufficient or inactive samples at baseline, and 44/45 (97.7%) had similar sampling results at 12 months. Of those with heavy and prolonged bleeding (mean 138.2 days bleeding during

**Table 4** Effect of estradiol valerate and norethisterone continuously on endometrial histopathology over three years

| *Endometrial histopathology* | *Visit 1 Pre-treatment* | *Visit 6 12 months* | *Visit 8 24 months* | *Visit 10 36 months* |
|---|---|---|---|---|
| Insufficient | 33 | 48 | 47 | 60 |
| Atrophic | 119 | 107 | 83 | 53 |
| Inactive | 10 | 2 | 8 | 7 |
| Secretory | 0 | 5 | 5 | 3 |
| Proliferative | 2 | 1 | 0 | 0 |
| Total | 164 | 163* | 143** | 123† |

*, One patient did not attend for sampling; **, twenty patients did not enter or complete year 2. One patient refused biopsy; †, no data on ten patients

**Table 5** Relationship between bleeding and endometrial histopathology during year 1

| | *No bleeding* | | *Heavy, prolonged bleeding** | |
|---|---|---|---|---|
| *Endometrial histopathology* | *Visit 1 Pre-treatment* | *Visit 6 12 months* | *Visit 1 Pre-treatment* | *Visit 6 12 months* |
| Insufficient | 6 | 17 | 1 | 1 |
| Atrophic | 38 | 27 | 10 | 11 |
| Inactive | 1 | 0 | 2 | 1 |
| Secretory | 0 | 1 | 0 | 1 |
| Proliferative | 0 | 0 | 1 | 0 |
| Total insufficient, atrophic and inactive | 45 (100%) | 44 (97.7%) | 13 (92.9%) | 13 (92.9%) |
| Total | 45 | 45 | 14 | 14 |

*, Defined as > 5 months bleeding with at least 1 cycle moderate or heavy

year 1, range 59–306), 13/14 (92.8%) had atrophic, insufficient or inactive samples at baseline and also at 12 months.

## Menopausal symptoms and bleeding

There was a very small minority of patients who continued to complain of menopausal symptoms, and we speculated that this might be due to non-compliance with the regimen, non-absorption of hormones, or receptor-resistance. We investigated estrogen levels to determine if there was any relationship between the continuance of menopausal symptoms, as exemplified by hot flushes and/or sweating, and bleeding pattern.

### *Hot flushes*

There were five patients of 163 who at the end of year 1 still complained of hot flushes. They had a mean of 1.2 flushes per day in the twelfth month of treatment; two were in the group of heavy and prolonged bleeders, with 61 and 306 days of bleeding, respectively, during year 1. The group had a mean estradiol level of 280.6 pmol/l and a mean of 77.2 days bleeding, which was not significantly different ($p = 0.35$) from the remainder of patients (mean estradiol level 245.1 pmol/l and mean bleeding 23.42 days) (see Table 6). In the twelfth month there were no days of bleeding in four patients and 28 days of bleeding in one patient. The endometrium was atrophic in four of these patients and insufficient in one.

### *Sweating*

There were 11 patients who had sweating attacks graded 50% or more in the 7 days prior to the month 12 assessment. They had a mean of 67.4% sweating; two of these patients were the same as above, being in the group of heavy and prolonged bleeders, with 61 and 306 days of bleeding, respectively, during year 1. This group of 11 patients had a mean estradiol level of 285.3 pmol/l and a mean of 48.32 days bleeding, not significantly different ($p = 0.104$) from the remainder of patients (mean estradiol level 243.4 pmol/l and mean bleeding 23.5 days) (see Table 6). In the twelfth month there were no days of bleeding in nine patients, 1 day in one patient and 28 days in one patient. The endometrium was atrophic in five of these 11 patients, insufficient in five and proliferative in one.

It was concluded that there was no significant relationship between the continuance of menopausal symptoms, as exemplified by hot flushes and sweating attacks, and estradiol levels or bleeding pattern.

## Adverse events

Eight patients discontinued because of bleeding during year 1, but there were no discontinuations due to bleeding during years 2 or 3. After bleeding/spotting, breast tenderness was the most common adverse event recorded, with 63 patients in year 1, but only four and three patients in years 2 and 3, respectively. There were no other prominent minor adverse events reported with any frequency.

Nine patients suffered fractures during the study period. These were fractures of toe, scaphoid, wrist, coccyx, clavicle (followed by deep vein thrombosis) and fibula.

The total number of complaints reported by completers, and the type of complaint, is shown in Table 7, which excludes patients with serious adverse events.

**Table 6** Relationship of menopausal symptoms and bleeding during year 1

| | *Patients with hot flushes at end year 1* | | | *Patients with sweating attacks graded 50% or more at end year 1* | | |
|---|---|---|---|---|---|---|
| | *Hot flushes* ($n = 5$) | *No hot flushes* ($n = 159$) | *p* | *Sweating* ($n = 11$) | *No sweating* ($n = 153$) | *p* |
| Bleeding in year 1 | | | | | | |
| mean days | 77.2 | 23.42 | | 48.32 | 23.5 | |
| median days | 14.0 | 8.00 | 0.3496 | 18.00 | 8.0 | 0.1045 |
| Estradiol levels | | | | | | |
| mean | 280.6 | 245.1 | | 285.3 | 243.4 | |
| median | 237.0 | 236.0 | 0.7110 | 298.0 | 236.0 | 0.3209 |

*p*, Wilcoxon difference of medians

**Table 7** Number of adverse events reported each year by patients who completed the study

| | *Year of study* | | |
|---|---|---|---|
| *Common adverse effects* | *1* ($n$ = 164) | *2* ($n$ = 144) | *3* ($n$ = 133) |
| Bleeding/spotting | 91 | 60 | 24 |
| Breast tenderness | 63 | 4 | 3 |
| Fracture | 7 | 1 | 1 |
| Joint/bone pain | 6 | 3 | 6 |
| Breast lump | 2 | 4 | 2 |
| Weight gain | 10 | 5 | 2 |
| Breathlessness | 3 | 0 | 1 |
| Menopausal symptoms | 4 | 1 | 5 |
| Ovarian cysts | 1 | 1 | 4 |
| Abnormal smear | — | 2 | — |
| Hypertension | 4 | 4 | 3 |
| Palpitations | 5 | 3 | — |
| Phlebitis | 3 | — | — |
| Stomach pain | 2 | 2 | — |
| Other adverse effects | 105 | 53 | 34 |
| Total | 306 | 143 | 85 |

There were seven serious adverse events in completers during year 1. In years 2 and 3 there were eight and nine serious adverse events, respectively. Of major clinical concern were two patients who developed symptoms of ischemic heart disease, and one each with breast carcinoma, adenocarcinoma of the ovary, carcinoma of the pancreas, squamous cell carcinoma of the skin and cervical carcinoma *in situ*. In addition, one patient was found to have chronic lymphatic leukemia which on review had been present prior to therapy. No definite relationship to drug therapy was considered likely for any of the serious adverse events. The details of these are given in Table 8.

In non-completers during years 1, 2 and 3 there were four, three and one serious adverse events, respectively; of particular note was cervical carcinoma *in situ*, carcinoma of the pancreas (symptoms which on review were present before therapy), adenocarcinoma of the ovaries and carcinoma of the breast. Further data are given in Table 9. The relationship to therapy in all these cases was improbable or uncertain.

### Adverse events and relationship to other observations

The results of those patients who had serious adverse events were further analyzed to determine if there was any relationship with bleeding pattern or endometrial histology.

Of the 24 patients (completers) with serious adverse events, no bleeding occurred at the end of the year in which the patient had complained of the adverse event in 21 patients, and the remaining three had only 8, 6 and 5 days bleeding per month. The number of patients with no bleeding is lower than that for other completers although an exact comparison is complicated by the shorter time on therapy for those with serious events.

Endometrial histology results in 22 of these patients for whom data were available showed atrophy in 14, insufficient in seven and secretory in one. These results were similar to those obtained for the other patients.

## DISCUSSION

### Menopausal symptoms

Significant improvements in menopausal symptoms were observed following daily treatment with an oral combination of estradiol valerate 2 mg and norethisterone 0.7 mg. This is in agreement with the findings for estrogen alone[14,15] or similar combined therapy[16]. The abolition of hot flushes and night sweats in most patients was as expected from estrogen in a dose of 2 mg daily. The addition of norethisterone continuously did not appear to have an adverse effect on symptom response as observed in an uncontrolled study, as expected from the fact that norethisterone on its own has been shown in a placebo-controlled study to cause a marked amelioration of hot flushes and night sweats in postmenopausal women[17].

It was reassuring that less explored symptoms such as depression, libido and ability to cope also improved significantly.

### Bleeding

Nearly 88% of patients were bleed-free by the end of the study. This percentage would have been higher if those women who were bleeding at 6 months had been discontinued from the study, since a number of these continued to bleed throughout. It is apparent that women who bleed heavily, or continuously, for up to the first 6 months of therapy, have a higher risk of continuing to bleed on a long-term basis, and may not be suited to this form of therapy.

However, individual variation was quite wide, with some patients who bled for the first 6 months having little trouble thereafter, whilst on the other hand, a few patients with no or only little bleeding during the first year had severe and sometimes prolonged bleeding subsequently.

The analysis of bleeding by duration since the menopause confirmed empirical observations in that continuous combined therapy should, in

**Table 8** Serious adverse events during treatment in completers

| *Condition* | *Month at onset or diagnosis* | *Duration of condition* | *Comment* |
|---|---|---|---|
| *Year 1* | | | |
| Phlebitis right leg | 4 | 1 month | no further details – no complaints at later visits; patient continued into 2nd year of study |
| Lump left breast | 5 | 2 months | removed – breast swelling benign; patient continued into 2nd year of study |
| Phlebitis left leg | 5 | 2 months | no further details – no complaints later; patient continued into 2nd year of study |
| Breast lumpiness | 5 | 3 months | mammography normal; diagnosed as benign swelling; patient continued into 2nd year of study |
| Deep vein thrombosis (after fracture left clavicle) | 6 | not stated | anticoagulant (warfarin) for 3 months; history of possible deep vein thrombosis at age 24 years; patient continued into 2nd year of study |
| Blackout | 12 | minutes | one episode; cause unknown; no previous history; patient continued into 2nd year of study |
| Jaundice: gallstones | 12 | 24 h | cholecystectomy 3 weeks later confirmed gallstones |
| *Year 2* | | | |
| Squamous cell carcinoma of skin on forehead | Prior to therapy | 3.5 years | recent treatment with radiotherapy |
| Anginal episodes | 13 | 2 episodes | treated with isosorbide and Diltiazem |
| Celiac disease | 16 | 6 months | gluten free diet; iron therapy |
| Giant cell tumor of tendon sheath | 17 | 0 | diagnosed as nodular synovioma; operated |
| Left ovarian cyst | 19 | — | under investigation |
| Small lump left breast | 20 | — | followed by serial mammograms |
| Maturity onset asthma | 20 | 4 months | treatment with prednisolone, theophylline, Ventolin, Becotide |
| Abnormal cervical smear | 20 | 0 | treated with colposcopy and laser |
| *Year 3* | | | |
| Ovarian cyst | Prior to therapy | 6 years | assumed to be the same cyst that had been under observation since 1987 |
| Chronic lymphatic leukemia | Prior to therapy | 3 years | on review, high white cell count prior to start of Climesse |
| Hysteroscopy for endometrial polyp and fibroids | 24 | unknown | hysteroscopy, removal of endometrial polyp and uterine fibroid |
| Left retinal hemorrhage | 27 | 2 months | 2 episodes – month 27 then month 34; received laser treatment |
| Dyspnea, rib costochondritis, chest discomfort | 29 | 2 days | admitted to hospital – nil found |
| Palpitations/tachycardia | 33 | 3 h | paroxysmal atrial tachycardia queried |
| Chest discomfort – ischemic heart disease | 34 | no data | coronary angiogram confirmed triple vessel disease; had coronary artery bypass graft; good recovery; continued on therapy |
| Abnormal liver function tests | 36 | unknown | CT liver scan normal; repeat liver function tests; letter to general practitioner |
| Carcinoma left breast | Post Climesse study | unknown | discovered after the end of the trial by follow up mammography; immediately referred for surgery |

**Table 9** Serious adverse events in non-completers

| *Serious adverse event* |
|---|
| *Year 1* |
| Abnormal cervical smear; diagnosed as carcinoma *in situ*; Climesse stopped owing to laser therapy to cervix |
| Deep vein thrombosis occurred post-operatively; Climesse stopped as precaution |
| Carcinoma pancreas; on chemotherapy; symptoms began before Climesse but not then obvious |
| Bladder obstructive enlargement; stress incontinence and frequency before Climesse |
| *Year 2* |
| Superficial venous thrombosis; left ankle fracture 2 years before |
| Pelvic mass – adenocarcinoma of ovaries |
| Carcinoma left breast |
| *Year 3* |
| Migraine attacks – severe, incapacitating and more frequent than previously |

general, be restricted to women who are 2 years or more postmenopausal.

Analysis of the relationship between menopausal symptoms at the end of year 1, and bleeding, revealed that patients who continued with hot flushes and sweating attacks did not have a significantly greater amount of bleeding in the first year of therapy than those without symptoms. Analysis of the estradiol levels of these patients, and comparison with the remaining patients, showed that those with symptoms did not have significantly different estradiol levels than those without.

It was reassuring that, in this study, patients requiring investigation for persistent bleeding showed no endometrial abnormality, but we are aware that the presence of polyps or fibroids prior to treatment may be a factor in persistent or heavy bleeding[18].

The bleeding profile at 3 months, with 84% having amenorrhea or light spotting, was very similar to that of Kliofem (82%). Thus the lower dose of norethisterone (Kliofem contains norethisterone acetate 1 mg daily) remains adequate to ensure low bleeding as well as endometrial suppression.

## Endometrium

The finding with Climesse of atrophic, insufficient or inactive endometria in 157 of 163 samples at the end of 12 months' treatment, and similar numbers at the end of 24 and 36 months' treatment, indicates a strong progestogenic effect on the endometrium. The five samples (and three at the end of 36 months) showing a secretory pattern also indicate a progestogenic effect.

These results may be compared with those obtained when an identical amount of norethisterone is added sequentially. Thus the results obtained by Whitehead and Fraser[7] with norethisterone 0.7 mg added for 10–12 days to Premarin® (Wyeth) were that out of 26 samples, 24 were non-secretory or were early secretory, one was late (full) secretory and in one there was insufficient sample. On the basis of their results, Whitehead and Fraser felt able to recommend norethisterone 0.7 mg given sequentially as a dose that can be recommended for widespread use.

The longer duration of progestogen dosing with Climesse (28 days) compared to the dosing by Whitehead and Fraser (10–12 days) gives theoretical reassurance concerning endometrial safety, while the results actually observed in 163 samples at the end of 12 months, and 143 and 133 samples at the end of 24 and 36 months, respectively, give practical evidence of the adequacy of the progestogenic effect. It is also reassuring in that heavy or prolonged bleeding in these patients was not associated with the development of endometrial abnormalities.

## Breast carcinoma

Breast carcinoma was diagnosed in two patients. In one patient, who at the start of the study was aged 48 years and was 17 months' postmenopausal, a carcinoma was discovered on mammography after she completed all three years of the study; she was referred for therapy. In the second patient, who was 53 years of age and 12 months' postmenopausal, an invasive ductal carcinoma was diagnosed after 15 months of the study; she was discontinued from the trial and referred for excision and chemotherapy.

The mean age of the cohort at the start of the study was 55.7 ± 6.2 years, and the recruited cohort of 206 patients comprised, with completers and

non-completers, a total of 468.3 woman-years of tablet-taking. Morbidity data from the UK Office for National Statistics for carcinoma of the female breast[19] give an expected value, age-weighted to the equivalent ratio in this study, of 250.9 per 100 000 population registered per annum. Therefore a population of 468.3 will give rise to an expected value of 1.17 breast carcinomata in any one year. The observed value of two breast carcinomata occuring during the course of this study fits the expected value, and is in accordance with both the results of studies which have observed no increase in risk[20–22] and those which reported an increase in the relative risk for short-term therapy of 1.4 or thereabouts[23,24]. No conclusion can therefore be drawn about a putative relationship to drug therapy.

### Thromboembolism

Two patients reported deep vein thrombosis during therapy. In one patient, aged 59 years, the deep vein thrombosis occurred after fracture of the left clavicle at the sixth month of therapy. Nevertheless, she continued therapy and completed the 3-year study without further incident. A second patient, also aged 59 years, developed deep vein thrombosis post-operatively after 12 months, and therapy was stopped as a precaution. Neither patient was overweight.

Current users of HRT are reported to have a risk of venous thromboembolism two or three times greater than for age-matched non-users[25–27]. Both of our patients had antecedent causes for thrombosis although a possible causative role for HRT in this setting cannot be excluded. Detailed results on coagulation factors in all patients will be reported separately.

## CONCLUSIONS

The combination of estradiol valerate 2 mg and norethisterone 0.7 mg given daily, orally and continuously to postmenopausal women leads to significant improvement in menopausal symptoms in nearly all patients. Two months after the start of therapy, hot flushes, sweating, vaginal dryness, tenseness and irritability, and depression showed significant and clinically important improvements. Libido and lack of ability to cope were also significantly improved, but not until month 4.

The mean incidence of bleeding declined from the start of the study, and the combination led to amenorrhea in most patients. Significantly less bleeding was observed in patients who were more than two years postmenopausal as compared to patients who were 6–24 months postmenopausal. Heavy or continuous bleeding that occurred in a minority of patients was not related to endometrial histopathology. Investigation of the small numbers of patients who continued with hot flushes or sweating attacks showed no relationship with estradiol levels nor bleeding pattern.

Although the combination therapy was well tolerated, serious adverse effects were reported, including a number of patients with carcinoma which were not in significantly greater incidence than expected, and no definite relationship to drug therapy was considered likely.

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