The effect of a change in the dose of trimegestone on the pattern of bleeding in estrogen-treated post-menopausal women: 6 month extension of a dose-ranging study

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BACKGROUND: Abnormal bleeding pattern is one major reason for non-compliance with hormone replacement therapy (HRT) in post-menopausal women. We have previously documented that the dose of trimegestone is the main determinant of the pattern of bleeding in women treated with estradiol (E₂) and sequential combined trimegestone administered in four doses. The objectives of this study were to test the effect of changing the dose of trimegestone and the duration of treatment on the pattern of bleeding in these women who then entered a 6 month extension phase where a single dose of trimegestone was given sequentially combined with E₂. METHODS: The menstrual diaries of 134 post-menopausal women who completed a dose-ranging study of trimegestone and then entered a 6 month extension phase were analysed. In the 6 month extension study, all women were given one dose of trimegestone (0.25 mg) in a sequential fashion (day 15–28) combined with continuous E₂ (2 mg/day). RESULTS: Women who had received trimegestone 0.25 mg/day during the first 6 months experienced no change in the bleeding pattern in the 6 month extension. Women who had been treated with 0.5 mg/day dose experienced earlier onset, and more prolonged bleeding (P < 0.0001) following the change to 0.25 mg/day. Women who previously received trimegestone doses of 0.05 and 0.1 mg experienced a later onset of bleeding, which was lighter and of shorter duration (P < 0.001) during the extension phase as compared with the first 6 months. CONCLUSION: The dose of trimegestone, and not the duration of treatment, appears to be the important determinant of the pattern of bleeding in post-menopausal women on this HRT regimen.

Key words: endometrial bleeding/HRT/menstrual diaries/trimegestone

Introduction
There is always a need for a hormone replacement therapy (HRT) that relieves symptoms of estrogen deficiency yet causes minimal adverse events. Only 50–60% of women prescribed HRT continue to take it beyond 1 year (Coope and Marsh, 1992). One of the main causes of non-compliance in peri- and post-menopausal women is withdrawal bleeding (Wren and Brown, 1991; Ravnikar, 1992; Faulkner et al., 1998).

Because of intermittent ovarian activity, the use of continuous combined and gonadomimetic therapies is not recommended until either 12 months have elapsed since the last menstrual period or the woman has reached 54 years of age. Thus, peri- and early post-menopausal women will need a sequential therapy and a predictable light bleed of short duration is likely to improve continuance.

Various strategies are available to try to achieve this. Reducing the dose of estrogen has been suggested (Li et al., 1992), but this may result in a recurrence of symptoms of estrogen deficiency, and lower estrogen doses may not be adequate to protect against bone loss in the peri- and early post-menopausal woman.

Extending the duration of progestogen treatment is associated with a reduction in the incidence of abnormal bleeding in controlled studies (Staland, 1981; Mattsson et al., 1982), but whether this is simply due to withdrawal of patients with bleeding problems is not clear. Increasing either the dose or duration of progestogens carries inherent problems due to a potentially higher incidence of progestogenic adverse effects.

Trimegestone is a novel norpregnane progestin with potent progesterone receptor and very low androgen receptor affinities, and no detectable affinity to estrogen receptors (Philibert et al., 1999). These properties make trimegestone suitable for combination with estrogen in HRT regimens and in theory minimize the androgenic adverse effects.

In a previous study, we have reported different bleeding patterns with different doses of trimegestone (Al-Azzawi et al., 1999), where the lower doses of trimegestone were associated with earlier and variable mean day of onset of bleeding with heavier and more prolonged bleeding compared with the higher doses. The aims of this study were firstly to assess whether the effect of changing the dose of trimegestone on the pattern
of bleeding is dependent on the dose of trimegestone in the sequential combined HRT regimen, and secondly to determine the effect of the duration of use on the pattern of bleeding in women who remained on the same dose of trimegestone.

Materials and methods

We recruited healthy women aged 45–65 years with an intact uterus who were at least 6 months amenorrhoeic. The study protocol was approved by the local ethics committees and all patients gave informed consent. All had either taken HRT for more than 2 years, had taken HRT for at least 1 year with pre-treatment FSH and E2 levels within the post-menopausal range, or had been amenorrhoeic for at least 6 months with FSH and E2 levels within the post-menopausal range. Previous use of an E2 implant was an exclusion criterion. Tests of liver and renal function were performed and those women with abnormalities were excluded. All women over the age of 50 years were required to have had a normal mammogram within 3 years prior to entry, and all women were required to have had a normal cervical smear within 6 months prior to study entry.

Initially, treatment was prescribed for six cycles. Assignment to treatment was random using SAS statistical package (SAS Institute Inc., Cary, NC, USA). The four doses of trimegestone were randomized on a 1:1:1:1 basis. Women were numbered consecutively in the order in which they entered the study. Each cycle consisted of oral micronized estradiol (RU 3499; Hoechst Marion Roussel, Romainville, France) 2 mg/day for 28 days and one of four doses of trimegestone tablets (0.05, 0.1, 0.25 or 0.5 mg per day) from day 15 to day 28 of each treatment cycle, for six cycles. The results of this 6 month study have already been published (Al-Azzawi et al., 1999). Women then entered an extension phase, which also lasted for 6 months. The E2 was prescribed in an identical fashion but all patients took trimegestone at one dose of 0.25 mg per day for days 15–28 of each cycle in the extension phase.

During the 6 month extension study women were asked to complete diaries for each treatment cycle in which the severity of the bleeding during the progesteron-associated bleeding (PAB) was subjectively scored as 0 = no bleeding, 1 = spotting, 2 = slight bleeding, 3 = moderate bleeding, and 4 = heavy bleeding. The total bleeding score (TBS) was taken as the sum of the daily scores in each cycle. At each visit diaries were collected and were checked for accuracy and completeness. These diaries also served as an additional parameter in the Vabra curette at baseline and after 6 and 12 months of the study.

A bleeding episode was defined as the longest bleeding episode which started on day 1 and lasted for ≥2 days with at least one clear day before and after. The PAB was defined as the longest bleeding episode which started between day 22 of one cycle and day 7 of the next treatment cycle, inclusive. All other bleeding episodes were defined as intermenstrual bleeding (IMB).

Only completed diaries were analysed for the purposes of this study. The bleeding data in cycles in which the endometrial biopsy was taken were excluded. The day of commencement of the estrogen phase of the cycle was defined as day 1.

General, breast and pelvic examinations were performed at baseline prior to commencement of the initial 6 months study and were repeated prior to the extension phase and had to be normal to allow the patient’s inclusion. An endometrial biopsy was obtained using the Vabra curette at baseline and after 6 and 12 months of the study. Patients were excluded if the histology showed any evidence of hyperplasia or cancer. Two pathologists, who were blinded to the dose of trimegestone, evaluated all endometrial biopsies independently.

Statistics

Data were collected on up to 13 cycles (1 year) for each woman and these repeated measures were analysed using mixed models. For continuous data, the residual maximum likelihood (REML) was used (Patterson and Thompson, 1971) to fit the model. For binary data, a generalized linear mixed model with binomial errors was used (Breslow and Clayton, 1993). Calculations were made using Genstat (Genstat, 1993). Patient data that were not collected separately for each cycle were analysed using analysis of variance or the χ²-test.

Results

A total of 266 women were randomized to one of the four doses of trimegestone and 203 women completed the first six cycles of treatment. Of these, 134 women elected to enter the extension phase of the study and to receive one dose of trimegestone (0.25 mg) for a further six treatment cycles and 107 women completed the extension study.

Women entering the extension study had an overall mean (± SD) age of 52.7 ± 5.4 years, a weight of 65.3 ± 9.5 kg, a height of 161.5 ± 6.7 cm and a body mass index (BMI) of 25.0 ± 3.3 kg/cm². There were no statistically significant differences between the initial and the extension study populations in terms of age, race, height, weight, BMI and smoking habits. Twenty-seven women did not complete the extension phase of the study. Fifteen withdrew because of adverse events, two were withdrawn for violating the protocol, six women withdrew for no apparent reason, and four were lost to follow up. Table I shows the number of women who recorded adverse effects during the extension study.

Table I. The incidence of adverse effects experienced during the extension study

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>AER (n)</th>
<th>SAE (n)</th>
<th>AED (n)</th>
<th>Dose (mg)</th>
<th>AER (n)</th>
<th>SAE (n)</th>
<th>AED (n)</th>
<th>Dose (mg)</th>
<th>AER (n)</th>
<th>SAE (n)</th>
<th>AED (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>29</td>
<td></td>
<td></td>
<td>0.1</td>
<td>32</td>
<td></td>
<td></td>
<td>0.25</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Breast pain</td>
<td>12</td>
<td>4</td>
<td>1</td>
<td>14</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bloatedness</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>13</td>
</tr>
</tbody>
</table>

AER = number of women in whom adverse events were recorded; SAE = number of women in whom severe adverse events were recorded; AED = number of women in whom study medication was withdrawn during the extension phase.

Trimegestone and post-menopausal bleeding patterns

events (AER), severe adverse events (SAE), and the number of women in whom study medication was withdrawn (AED) during the extension phase. The data are presented according to trimegestone dose used in the initial 6 month study. The same woman may appear in all three categories (AER, SAE and AED). There were no statistically significant differences between the numbers of women from each previous trimegestone dose group experiencing AER, SAE and AED, nor was there a statistically significant difference between the number of women from each previous trimegestone dose group who withdrew during the extension phase. There were three serious adverse events necessitating medical investigation and withdrawal from the study: one patient had a myocardial ischaemia, another developed facial palsy and the third developed appendicitis.

Evaluation of the bleeding episodes was based on the data collected from 718 menstrual diaries completed by 134 women during the first 6 months and 628 completed diaries collected from the same women during the extension phase of the study. Only completed diaries were included in the analysis and to the day of withdrawal for women who did not complete the study.

**Mean day of onset of progestogen-associated bleeding**

The mean day of onset of PAB in women on the lower doses of 0.05 and 0.1 mg, which were 25.2 and 26.4 respectively in the first 6 cycles, changed in the following six cycles and occurred later, i.e. after the end of the progestogen phase of treatment (28.8 and 29.0; \( P = 0.0001 \) and \( P = 0.0001 \) respectively, Figure 1A). Women who continued on the 0.25 mg trimegestone showed no statistically significant change in the mean day of onset of the PAB; however, women on the 0.5 mg dose of trimegestone who had a mean day of onset of the PAB on 30.9 day in the first six cycles experienced an earlier mean day of onset of the PAB, though it still occurred after the end of the progestogen phase (29.0, \( P = 0.0001 \); Figure 1B).

**Duration of progestogen-associated bleeding**

Women on the lower doses of trimegestone, 0.05 and 0.1 mg in the first 6 months who had a mean duration of PAB of 7.01 days and 6.48 days respectively, experienced shorter episodes of PAB when they received the higher dose of 0.25 mg (5.7 and 5.2, \( P = 0.0001 \) and \( P = 0.001 \) respectively; Figure 2). Women who continued on 0.25 mg dose experienced no significant change in the PAB duration, while women who had bled for only 4.6 days on the 0.5 mg dose during the first 6 months, developed longer episodes of PAB of 5.4 days on changing to the lower dose of trimegestone (\( P = 0.001 \)).

**Severity of the progestogen-associated bleeding (TBS)**

Women on the trimegestone doses of 0.05 and 0.1 mg who had mean TBS of 15.5 and 14.3 respectively in the first six cycles experienced lighter bleeding in the second 6 months, when they received the 0.25 mg of trimegestone (TBS = 11.8 and 12.6 respectively, \( P = 0.0001 \) and \( P = 0.001 \) respectively; Figure 3). There was no significant change in the severity of the bleeding in women who continued on the 0.25 mg dose (11.6 and 11.4). TBS increased in women who received the 0.5 mg trimegestone in the first 6 months when changed to 0.25 mg in the extension study (TBS = 10.6 and 11.5 respectively) but the increase was not statistically significant.

**Incidence of the IMB**

There were six episodes of IMB among women who continued on the same dose of 0.25 mg in the extension phase compared with two in the first 6 months (Table II). In the 0.5 mg dose group, there was significant reduction (\( P = 0.02 \)) in the incidence from 10 in the first 6 months to only one in the extension phase, while there was no significant difference in

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**Figure 1.** (A) Mean and range day of onset of progestogen-associated bleeding (PAB) in the 0.05 and 0.1 mg groups during the first 6 months, compared with the mean day of onset of the PAB in the second 6 months where only one dose of trimegestone (0.25 mg) was administered. Red circles are mean day of onset of the PAB in the individual woman in the first 6 months, blue triangles are mean day of onset of the PAB in the individual woman in the second 6 months. (B) Mean and range day of onset of PAB in the 0.25 and 0.5 mg groups during the first 6 months, compared with the mean day of onset of the PAB in the second 6 months where only one dose of trimegestone (0.25 mg) was administered. Red circles are mean day of onset of the PAB in the individual woman in the first 6 months, blue triangles are mean day of onset of the PAB in the individual woman in the second 6 months.
Trimegestone and post-menopausal bleeding patterns

Figure 2. Duration of the progestogen-associated bleeding (PAB) in the four dose groups in the first 6 months compared with the second 6 months. Red circles are duration of the PAB in the individual woman in the first 6 months, blue triangles are duration of the PAB in the individual woman in the second 6 months.

Figure 3. Severity of the progestogen-associated bleeding (PAB) in the four dose groups in the first 6 months compared with the second 6 months. Red circles are total bleeding score (TBS) in the individual woman in the first 6 months, blue triangles are TBS in the individual woman in the second 6 months.

The incidence of IMB among women in the lower dose groups when they continued in the extension phase.

Endometrial histology
The histological assessment of the endometrium at the end of 6 months showed secretory changes in 96% of the biopsies, with one case of simple hyperplasia in the 0.5 mg dose group. The histology in the extension study showed secretory changes (96.8%), inactive endometrium (2.1%) and one case of simple hyperplasia in an endometrial polyp in the group which was previously receiving 0.5 mg (1.1%, Table III).

Discussion
This study showed that the dose of trimegestone was the major determinant of the pattern of bleeding. In the extension study, when the dose of trimegestone was fixed at 0.25 mg/day, women who previously experienced abnormal bleeding patterns on the trimegestone doses of 0.05 and 0.1 mg experienced a later mean day of onset of bleeding which was lighter and of shorter duration, while women who were on the 0.5 mg dose in the first 6 months regressed to experience earlier mean day of onset of the bleeding episode, and prolonged bleeding during the extension phase of the study.

The duration of progestogen administration for 10–14 days appears to be an important factor in protecting the endometrium (Sturdee et al., 1978; Whitehead, 1978) against the increased risk of endometrial hyperplasia and cancer induced by unopposed estrogens. Recently, it has been reported that in sequential combined estrogen and progestogen regimens, the use of the progestogen for <16 days per treatment cycle was associated with an increase relative risk of endometrial hyperplasia and carcinoma (Weiderpass et al., 1999). The type of progestogen administered may also have an influence on endometrial protection as testosterone-derived progestogens conferred a higher endometrial protection than progesterone-derived progestogens (Weiderpass et al., 1999).

In this study, trimegestone had an acceptable endometrial safety effect. In one woman in the 0.5 mg dose group a case of simple hyperplasia was observed in a polyp, with variable secretory changes in the rest of the endometrial sample at the end of the extension phase of the study. Another case of simple hyperplasia was documented in the 0.5 mg trimegestone dose group in the first 6 months (Al-Azzawi et al., 1999). These two cases of simple hyperplasia are well within the incidence quoted for untreated post-menopausal women (Kurman, 1994).

A link between inadequate endometrial secretory changes and the occurrence of bleeding before the end of the progestogenic phase in sequential combined HRT has been suggested (Padwick et al., 1986). This observation was challenged by a larger study of women receiving different HRT regimens (Sturdee et al., 1994), in which no correlation was found between the day of onset of bleeding and endometrial histology among 413 women who had used sequential combined HRT regimens for 3 months. This concurred with our findings in a histomorphometric analysis of endometrial samples obtained at the end of the dose-ranging study, where no discernible dose-related histological features were identified (Wahab et al., 1999).

In the extension study, the dose of 0.25 mg was chosen and not the 0.5 mg based on the premise that the lowest dose of the progestin required to demonstrate clinical efficacy should be used, and to test the assumption that with longer duration of use bleeding pattern might improve.

In women on the 0.25 mg dose of trimegestone who continued on the same dose in the extension phase, there was no significant change in the incidence of abnormal bleeding patterns with time. However, there was a higher incidence of IMB compared with the first 6 months, a finding difficult to explain in view of the overall small number of women with IMB episodes.

The 0.5 mg dose was associated with higher incidence of IMB in the first 6 months, but when these women completed the extension phase of the study, a lower incidence of IMB
was noted. This reduction in the incidence of IMB may be more apparent than real, since the mean day of onset of PAB became earlier at day 29.0 instead of day 30.9. This further supports our previous interpretation that the high incidence of IMB in this dose group, during the first 6 months, may be due to a higher incidence of delayed bleeding extending outside the PAB window.

In conclusion, this study has shown two important therapeutic features of this new progestogen when used in sequential combined HRT regimens. First, the dose of trimegestone was a major determinant of the pattern of bleeding in postmenopausal women treated with this sequential combined HRT regimen, and the change of dose altered all parameters used to assess the bleeding episodes. Second, apart from IMB in a small number of women, there was no change in the bleeding pattern with duration of treatment.

Acknowledgement
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References


Table II. The change in the incidence of intermenstrual bleeding (IMB) as a result of changing the dose of trimegestone to 0.25 mg in the extension phase of the study

<table>
<thead>
<tr>
<th>Cycle no.</th>
<th>No. of IMB episodes</th>
<th>No. of IMB days</th>
<th>Mean no. of IMB episodes</th>
<th>Mean no. of IMB days</th>
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</thead>
<tbody>
<tr>
<td>0.05 mg</td>
<td>0.1 mg</td>
<td>0.25 mg</td>
<td>0.5 mg</td>
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<tr>
<td>1–2</td>
<td>0</td>
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<td>0</td>
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</tr>
<tr>
<td>2–3</td>
<td>1</td>
<td>1</td>
<td>1</td>
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</tr>
<tr>
<td>3–4</td>
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</tr>
<tr>
<td>4–5</td>
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<td>6</td>
<td>1</td>
<td>1</td>
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<tr>
<td>5–6</td>
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<td>8</td>
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<tr>
<td>Change in the dose of trimegestone to 0.25 mg</td>
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<td>6–7</td>
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<td>7–8</td>
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<td>10–11</td>
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</table>

Data are presented in groups according to the dose of trimegestone used in the first 6 months.

Table III. Histological findings at the end of the extension study (12 months)

<table>
<thead>
<tr>
<th>Total</th>
<th>Total no. of treated women</th>
<th>No. of IMB episodes</th>
<th>No. of IMB days</th>
<th>Mean no. of IMB episodes</th>
<th>Mean no. of IMB days</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>134</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrial biopsy, n (%)</td>
<td>Inactive</td>
<td>2 (2.1)</td>
<td>Early secretory</td>
<td>2 (2.1)</td>
<td>Late secretory</td>
</tr>
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