Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy

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ABSTRACT

Oestrogen therapy is the gold standard treatment for hot flushes/night sweats, but it and oestrogen/progestin are not suitable for all women. MPA (medroxyprogesterone acetate) reduces hot flushes, but its effectiveness compared with oestrogen is unknown. In the present study, oral oestrogen [CEE (conjugated equine oestrogen)] and MPA were compared for their effects on hot flushes in a planned analysis of a secondary outcome for a 1-year randomized double-blind parallel group controlled trial in an urban academic medical centre. Participants were healthy menstruating women prior to hysterectomy/ovariectomy for benign disease. A total of 41 women [age, 45 (5) years [value is mean (S.D.)]] were enrolled; 38 women were included in this analysis of daily identical capsules containing CEE (0.6 mg/day) or MPA (10 mg/day). Demographic variables did not differ at baseline. Daily data provided the number of night and day flushes compared by group. The vasomotor symptom day-to-day intensity change was assessed by therapy assignment. Hot flushes/night sweats were well controlled in both groups, one occurred on average every third day and every fourth night. Mean/day daytime occurrences were 0.363 and 0.187 with CEE and MPA respectively, but were not significantly different (P = 0.156). Night sweats also did not differ significantly (P = 0.766). Therapies were statistically equivalent (within one event/24 h) in the control of vasomotor symptoms. Day-to-day hot flush intensity decreased with MPA and tended to remain stable with CEE (P < 0.001). In conclusion, this analysis demonstrates that MPA and CEE are equivalent and effective in the control of the number of hot flushes/night sweats immediately following premenopausal ovariectomy.

INTRODUCTION

CEE (conjugated equine oestrogen) and other oestrogens provide effective treatment for hot flushes and night sweats: these are collectively called vasomotor symptoms. A systematic review of randomized double-blind placebo-controlled trials concluded that oestrogen therapy reduces the frequency of hot flushes and night sweats by 75% [1]. However, the use of oestrogen for menopausal treatment has become problematic. CEE with MPA (medroxyprogesterone acetate) therapy caused significantly

Key words: conjugated equine oestrogen (CEE), hot flush, medroxyprogesterone acetate (MPA), night sweats, randomized double-blind controlled trial, surgical menopause, vasomotor symptom.

Abbreviations: BMI, body mass index; CEE, conjugated equine oestrogen; CI, confidence interval; HDL, high-density lipoprotein; MPA, medroxyprogesterone acetate; RR, relative risk.

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more harm than benefit compared with placebo in primarily asymptomatic menopausal women in the Women's Health Initiative Randomized Controlled Trial [2]. In the oestrogen-only arm of the Women's Health Initiative, women who had undergone hysterectomy also received no benefit in preventing coronary heart disease and had an increase in stroke compared with placebo [3]. A meta-analysis of randomized controlled menopausal hormone therapy trials showed that oestrogen therapy over 5 years caused harm exceeding benefit in 1 out of 230 women aged 50–59 years [4], the age range in which most vasomotor symptoms are treated. Oestrogen therapy, even for severe vasomotor symptoms, is currently contraindicated for women with breast cancer, thrombophilies or active liver disease. Finally, largely asymptomatic menopausal women discontinuing oestrogen/progestin therapy after the Women's Health Initiative were almost 6 times more likely to experience moderate-to-severe hot flushes than were women randomized to placebo [5].

Hormone therapy was discontinued by half of the hormone-treated women in New Zealand and the U.S.A. following the results of randomized controlled hormone therapy trials [6–8]. Women over 65 years of age in Ontario also filled 32% fewer hormone prescriptions [9]; however, with the discontinuation of oestrogen, many women re-developed hot flushes. Therefore 18% of women report re-starting hormone therapy, and 76% of these for recurrence of severe hot flushes or night sweats [6]. Others reported intense hot flushes that alternate therapies did not adequately control [10].

Oral progestins, like oestrogens, have been shown to be effective for vasomotor symptoms in randomized placebo-controlled trials from the 1980s [11–14]. There are also a few head-to-head trials of progestins compared with oestrogens. Two such trials tested androgen-derived progestins and high doses of ethinyl oestradiol [15,16]. In one, ethinyl oestradiol and oestradiol/d-norgestrel were more effective than d-norgestrel alone, and all hormone arms were more effective than placebo [15]. In the other trial, although ethinyl oestradiol was effective and the results of the two hormone arms were not different, norethindrone also did not differ from placebo [16]. No randomized comparative trials for hot flushes have tested currently used doses of CEE and MPA.

Data to support the choice of a minimal clinically significant difference in vasomotor symptoms are scarce. However, in a review of data from a series of vasomotor symptom cross-over studies, Sloan et al. [17] found that those women who expressed a preference reported a median of 1.3 fewer hot flushes/24 h, whereas those who expressed no preference differed by 0.4 hot flushes/day. This observation, and clinical experience, led us to use a difference of one or fewer hot flush event/day as our criterion for equivalence. This is less than the criterion for improvement of 50% used by Sloan et al. [17], which corresponds to approx. two events/day in their highly symptomatic population [17].

The aim of the present study was to compare MPA at a luteal phase equivalent dose (10 mg/day) and CEE in a standard menopause dose (0.6 mg/day) for their effects in controlling the number and intensity hot flushes and night sweats (hot flushes during sleep). The treatments were hypothesized to be similarly effective. The present study analysed women's daily experience of day and night flushes during a 12-month trial starting from the time of hospital discharge following pre-/peri-menopausal hysterectomy and ovariectomy for benign disease.

**MATERIALS AND METHODS**

This was a randomized double-blind parallel group trial of two hormonal therapies taken daily [18]. The present analysis was a pre-planned analysis of a secondary end point in a randomized controlled trial examining bone mineral density changes [18]. The primary outcome variable was the number of hot flush/night sweat vasomotor symptom episodes/24-h period. A placebo arm was not included in the present study, because placebo-treated women lose bone rapidly following premenopausal ovariectomy [19]. The Human Ethics Committees at the University of British Columbia and participating hospitals approved the protocol. Prior to enrolment, all women provided written informed consent.

Women were enrolled between 1989 and 1991 and were randomized as described previously [18]. Briefly, women scheduled for hysterectomy with bilateral ovariectomy were identified from pre-operative lists at four teaching hospitals and one community hospital. Following permission from the operating gynaecologist, the study nurse visited each woman to provide information about the study and to screen women for eligibility. Participants were pre- or peri-menopausal women (who had menstruated within 4 months) and who were not using hormonal therapy. They had undergone hysterectomy with bilateral ovariectomy for a benign condition and had no contra-indications to hormone therapy [18].

Participants were assigned to one of the two therapies using a randomization table administered by the Vancouver General Hospital research pharmacist who dispensed the study medication and maintained the therapy assignment code. They received CEE at a dose of 0.6 mg/day or MPA at a dose of 10 mg/day, each dispensed in two identical powder-filled capsules taken once a day. Investigators remained blinded to the therapy assignment until completion of the data collection and construction of an accurate database.

Participants recorded their experiences in the Daily Menopause Diary©, an instrument with short-term reproducibility [20], that allowed documentation of both the number and the intensity of daytime hot flushes as...
well as night sweats that occurred during sleep. Participants were seen monthly over the first 6-month interval and then every 3 months until study completion.

Statistical analysis [21,22] used the number of vasomotor symptom episodes/24-h period as the primary outcome variable. The secondary outcome was the intensity of hot flushes/night sweats on a scale from 0–4. Possible explanatory variables for the number of hot flushes included BMI (body mass index; kg/m²), age at menarche and gynaecological age (years from menarche).

Primary analyses were based on calculations of the number of vasomotor symptoms/day following enrolment. To describe the relationship between the incidence of vasomotor symptoms and therapy, each woman’s follow-up was divided into a series of consecutive 1-month periods. The episode rate was calculated as the number of events divided by the total number of observed woman-days in that month for each woman. Poisson regression models with adjustment for overdispersion (S-PLUS version 6.1; Insightful) were used to quantify the relationship between treatment and vasomotor symptom rates by month. All of the variables were treated as fixed at their values at the start of the study. The Poisson log-linear regression modelled the number of vasomotor symptoms as a function of these variables, a mean value/month following enrolment by treatment category and with the logarithm of the observed patient-days included in the model as an offset to account for differential follow-up periods over participants. Corrections for overdispersion and within-patient correlation between the repeated events were included with the use of generalized estimating equations.

Equivalence testing of the two therapies for the control of vasomotor symptoms was performed using the null hypothesis that the difference in daily frequency of vasomotor symptoms (total of both day and night) was greater than one event/24-h period. Tests were two-tailed, and \( \alpha \) was set at 0.05. Changes in hot flush intensity from day-to-day and night-to-night by therapy assignment were also analysed using Markov chain modelling. This analysis provided the potential to track the progression of the hot flush intensity level (on a scale of 0–4) over time by treatment group.

RESULTS

A total of 41 women, whose mean (S.D.) age was 45 (5) years, were enrolled and randomized. The flow of participants through the trial is shown in Figure 1. Eligibility criteria and indications for hysterectomy with ovariectomy have been reported previously [18]. Only three women did not provide data for this analysis. One woman decided against participation immediately following randomization and without taking any of the study drugs. A second discontinued at 1 week because of difficulty swallowing the large gelatin capsules. The third was withdrawn at 4 months for acute hyperthyroidism, as this condition alters temperature control and is in the differential diagnosis of hot flushes. Most women completed at least 360 days; the early study withdrawals of five of the women are described in Figure 1. Within the period of data collection, Daily Menopause Diary® entries were 94 % complete. Thus data from 38 out of the 41 randomized participants contributed to this analysis.

Table 1 shows the baseline demographic characteristics of the participants. Women randomized to the CEE and MPA treatment groups did not differ with regard to any documented characteristics. Participant adherence by capsule count was > 90 % and equal by therapy [18].

Both CEE and MPA therapies were well tolerated following surgical menopause. Hot flushes and night sweats were generally well controlled in both groups. After the first 6 weeks, 45 % of the study population was free of daytime hot flushes and 30 % were free of night sweats. No participant experienced thrombophlebitis, myocardial infarction, stroke or breast cancer during the study (or a systematic 1-year follow-up; J. C. Prior, unpublished work). However, weight gain was nearly universal and averaged 3.2 ± 4.0 kg over the year and was significantly greater in the CEE group than in the MPA group [18]. One woman on MPA discontinued at 4 months with severe hot flushes and dyspareunia. Three women on CEE withdrew, despite good hot flush control, after 1–5 months with complaints of low energy, trouble sleeping and headaches. Data from these four discontinuing women were included in this analysis.

The mean rate of hot flushes was very low for the entire year, but was also somewhat variable over time. For both therapy groups, the overall mean rate was 0.282 hot flushes/day and 0.268 night sweats/night, which created a total mean of 0.556 vasomotor symptoms/24-h period. These rates were significantly affected by BMI, but not gynaecological age or age at menarche. The values show rates as adjusted for BMI. The mean overall daytime and night-time daily rates of hot flushes for women in the CEE arm are shown as a horizontal line in Figure 2. The mean and 95 % CIs (confidence intervals) for rates for each month on CEE therapy are superimposed upon that of the CEE-therapy mean (Figure 2).

The tendency for fewer vasomotor symptoms/day for those randomized to MPA was not statistically significant (24-h RR (relative risk), 0.74 (95 % CI, 0.27–2.00); daytime RR, 0.56 (95 % CI, 0.20–1.55); and night-time RR, 1.02 (95 % CI, 0.35–2.99)). A formal test of equivalence (defined as no greater than one vasomotor symptom event difference/24-h period) found the therapies were significantly equivalent \( (P < 0.01) \). Of the other covariates considered, only BMI was statistically significant for the number of overall and night-time hot flushes and was associated with an increase in the rate of 24-h overall, daytime and night-time hot flushes (overall RR, 1.19
Figure 1  The CONSORT figure for the randomized therapy trial comparing CEE (0.6 mg/day) with MPA (10 mg/day) as a therapy for vasomotor symptoms in women undergoing premenopausal ovariectomy for benign disease

The flow of individuals from initial screening and secondary eligibility through to enrolment and randomization to one of two therapies is shown. The number of women who contributed partial data or who were excluded from the analysis is also shown. VMS, vasomotor symptoms.

Other covariates considered included age at menarche [overall RR, 1.01 (95 % CI, 0.69–1.46); daytime RR, 1.07 (95 % CI, 0.78–1.49); and night-time RR, 0.97 (95 % CI, 0.61–1.53)] and gynaecological age [24-h RR, 0.98 (95 % CI, 0.90–1.07); daytime RR, 1.00 (95 % CI, 0.91–1.10); and night-time RR, 0.96 (95 % CI, 0.87–1.07)].

Vasomotor-symptom-free days were common in both therapies throughout this 1-year study. For women on CEE, 82 % of days and 85 % of nights were without hot flushes. For women on MPA, 90 % of days and 87 % of nights were without hot flushes.

Monthly patterns over the course of a year are shown in Figure 3. The difference and 95 % CIs between therapy arms for overall 24-h vasomotor symptoms, after adjusting for BMI, are plotted in Figure 3 (top panel). The bold horizontal line represents an equal experience by therapy. Values above zero indicate fewer hot flushes in the MPA arm. Figure 3 also shows the CEE–MPA hot flush rates for daytime and night sweat rates (Figure 3, middle and bottom panels respectively).

For the most part, rates of overall, daytime or night-time vasomotor experiences did not differ significantly between the CEE and MPA groups, with 1 month with a marginally significant difference during the year. The mean differences between CEE and MPA in hot flush numbers/day corrected for BMI are shown in Figure 3 as dotted horizontal lines, representing 0.277 vasomotor symptoms/24-h period (P = 0.30), 0.182 hot flushes/
Table 1  Baseline demographic data for women providing Daily Menopause Diary® records by random assignment to CEE (0.6 mg/day) or MPA (10 mg/day) therapy during a double-blind parallel trial of hot flushes and night sweats following premenopausal hysterectomy and ovariectomy

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CEE</td>
</tr>
<tr>
<td>n</td>
<td>18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43.8 (6.1)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.3 (8.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.3 (5.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 (2.8)</td>
</tr>
<tr>
<td>Menarche age (year)</td>
<td>12.4 (1.7)</td>
</tr>
<tr>
<td>Gynaecological age (year)</td>
<td>30.6 (6.6)</td>
</tr>
<tr>
<td>Time since surgery (days)*</td>
<td>6.3 (4.5)</td>
</tr>
<tr>
<td>Caucasian/Asian (n)</td>
<td>16/2</td>
</tr>
<tr>
<td>Missing data (% of days)</td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>8.0% (17.6%)</td>
</tr>
<tr>
<td>Night-time</td>
<td>8.5% (16.5%)</td>
</tr>
</tbody>
</table>

*Days following ovariectomy at which they were discharged from hospital and randomized therapy began.

Women experiencing a premenopausal ovariectomy tend to have more intense hot flushes/night sweats than women with natural menopause [23]. However, women in the present study, all of whom were treated from the day of hospital discharge, in general, did not develop troublesome symptoms. Only one perimenopausal woman reported experiencing hot flushes before enrolment. That the expected intense symptoms, as are usually reported in women with surgical menopause [10], were not experienced in the present study suggests that both therapies can be highly effective. The small differences in day and night hot flushes between therapies, 95% CIs around the differences in the rates of the two treatments and formal equivalence testing all indicate that CEE and MPA are similarly effective in controlling the number of hot flushes.

To our knowledge, this is the first randomized controlled trial to directly compare hot flush control with MPA and CEE. Randomized placebo-controlled trials from the 1980s have shown that MPA effectively reduced hot flushes [11–13]. Two previous studies that compared androgen-derived progestins with ethinyl oestradiol produced variable results. Dennerstein et al. [15] found d-norgestrel to be more effective than placebo, but less effective than oestrone or combined oestrogen and d-norgestrel. Nordin et al. [16] found that norethisterone was no more effective than placebo and less effective than oestrone in a 3-week study. These trials, however, are of limited current applicability because of the very high doses of ethinyl oestradiol that were used.

The strengths of the present study are its 1-year duration, its double-blind character and the completeness of the data analysed over 1 year. Furthermore, participation of initially pre-/peri-menopausal women, who were just discharged following bilateral ovariectomy and hysterectomy, eliminated any major differences in endogenous ovarian hormone levels that might have confounded the effects of therapy on hot flushes/night sweats.

It is not clear what triggers hot flushes and night sweats, but it has been assumed to relate to oestrogen exposure and decreasing oestrogen levels; it does not require elevated gonadotrophins [24]. Decreased serotonin and noradrenaline (norepinephrine) levels are implicated [25], hence the therapeutic use of agents acting through these neurotransmitters [26]. MPA may control hot flushes by different pathways from oestrogen. MPA, acting through hypothalamic mechanisms, modulates LH (luteinizing hormone) pulse frequency [27], increases core temperature [28] and stimulates respiration [29]. Thus MPA acts on the hypothalamus, the central site at which hot-flush generation is understood to occur.

One limitation of the present study was the lack of presurgical baseline data. Potential participants were identified using surgical slates and were only eligible for study enrolment following surgery. Given the major physiological changes caused by premenopausal ovariectomy...
Figure 2 Vasomotor symptoms (as rate/24-h period) over 1 year following premenopausal ovariectomy for benign disease

Month 1 is the month immediately following surgery and study enrolment. Points are estimated average daily rate for women in the CEE group (0.6 mg/day), adjusted for BMI, and shown with 95% CIs for each month. Analysis was by Poisson regression model with adjustment for overdispersion. Top panel, overall rate; middle panel, daytime only; and bottom panel, during sleep only. The grey horizontal lines represent the estimated daily average rate during CEE therapy during the full year.

itself and that all except one woman had never previously experienced hot flushes, it could be argued that inclusion of information from pre-operative baseline measurements, even if these were available, may not be entirely appropriate. However, investigating the usefulness of such measurements would have been helpful.

As far as possible, the present study resembles an intent-to-treat analysis. Only data from three randomized women were not analysed: one took no medication, one took it for only 1 week and the third had hyperthyroidism that developed during the first 4 months of the trial. Because hyperthyroidism may cause sweating and heat intolerance, her data were judged to be potentially confounded by her illness.

The use of MPA therapy for vasomotor symptoms may raise concerns about metabolic changes. Results from participants in the present randomized blinded 1-year trial are available to describe changes in weight, blood pressure, percentage body fat, lipids, electrolytes and hepatic and renal function during CEE compared with MPA therapy. Weight gain during CEE therapy exceeded that with MPA [18]. In addition, women recorded 16 other experiences daily, including depression, which we are analysing using factorial analysis (J. C. Prior, W. Mercer, C. L. Hitchcock and E. Kingwell, unpublished work).

One consideration in selecting MPA or CEE as therapy for menopausal hot flushes is the effect of each on venous thrombo-embolism, lipids, endothelial function, cardiovascular disease and strokes. Long-term placebo-controlled trials of MPA alone are needed but they are not available to date. The best analysis of available data suggests that oral CEE therapy doubled the relative risk for thrombosis [2,3], tripled it in older women with heart
Progestin and oestrogen are equal for hot flushes

Figure 3  Difference between the therapies in the daily rate of vasomotor symptoms
Points are the estimated difference in the daily rate of vasomotor symptoms/month between CEE (0.6 mg/day) and MPA (10 mg/day) with 95% CIs, adjusted for BMI. Analysis was by Poisson regression model with adjustment for overdispersion. There was no significant difference between the therapies, and the two therapies were statistically equivalent (within 1 event/day of each other; $P < 0.01$). Top panel, overall rate; middle panel, daytime only; and bottom panel, during sleep only. The bold horizontal lines represent equality. Positive values indicate fewer vasomotor symptoms for women randomized to take MPA. The dotted horizontal lines are the estimated average daily differences by therapy in hot flushes over the year in these women following premenopausal ovariectomy for benign disease.

disease [30] and quadrupled it in those with cancer. A multi-centre long-term trial of high dose MPA (1200 mg/day) in 42 women with advanced breast cancer showed no coagulation/fibrinolysis changes compared with chemotherapy-treated controls [31], suggesting no increased risk of thrombosis. Although supposedly cardioprotective, increases in HDL (high-density lipoprotein)-cholesterol occur with oral oestrogen therapy, but this lipid change did not prevent heart attacks in recent controlled trials [2,3,30]. MPA with CEE caused a significant, but probably not biologically important, decrease in HDL-cholesterol ([32], but see [32a]). Both progestin and oestrogen cause beneficial decreases in LDL (low-density lipoprotein) and total cholesterol; however, only oestrogen causes a detrimental increase in triacylglycerol (triglyceride) levels. Therefore the lipid changes of each, although different, appear similar in cardiovascular impact. Oestrogen causes improvements in endothelial function that may [33–35] or may not [36] be modified by varying doses of MPA. Multiple controlled studies have shown no effect of either hormone on blood pressure. The incidence of stroke was similar in the oestrogen-with-progestin and oestrogen-only arms of controlled trials [2,3], suggesting no excess risk of stroke from MPA therapy.

Whether or not MPA increases the risk of breast cancer is unknown, although data showing lower risk of breast cancer following pelvic surgeries, such as hysterectomy [37], suggest that the apparent increased risk of breast cancer with combined hormones compared with
oestrogen alone may represent confounding by indication. A large international case-control study has found no increased risk of breast cancer with depot MPA used for contraception [38].

In summary, in the present 1-year randomized double-blind study, both CEE, the gold standard, and MPA effectively and equivalently controlled night-time and daytime hot flushes in women treated immediately following premenopausal ovariectomy. This parallel therapy trial showed an equivalent control of the number of hot flushes and night sweats between oestrogen- and progestin-treated women. MPA caused a greater decrease in hot flush intensity change from day-to-day compared with CEE. For these reasons MPA offers an alternative to CEE treatment for intense hot flushes/night sweats in women for whom oestrogen is either contra-indicated or undesirable. This important study adds to the evidence-based information available to women and clinicians on effective treatment of vasomotor symptoms. Larger trials are required to confirm these findings.

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REFERENCES


© 2007 The Biochemical Society
36 Sanada, M., Higashi, Y., Nakagawa, K. et al. (2002) Combination therapy of low-dose medroxyprogesterone acetate and oral estrogen does not affect endothelial function in the forearm of postmenopausal women. Menopause 9, 360–366

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