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The use of micronized progesterone for menopausal hormone therapy, a clinical practice audit.

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Abstract

A clinical practice audit was undertaken to share an Australian experience of the use of micronized progesterone (mP) 100 mg daily as part of menopausal hormone therapy (MHT). Ninety-nine women attending a single practitioner were offered the option of mP as a component of MHT,

under the Australian Authorised Prescriber Scheme, over 2.5 years. Each of their files was independently audited. The mean age at commencement was 55.0 (SD 6.6) years. Of the 93 postmenopausal women, 7 were lost to follow-up, 18 discontinued and treatment was on-going for 68. The mean duration of treatment for those ongoing was 1.7 (SD 0.5) years and for those who discontinued, 0.6 (SD 0.6) years. The most common side effect was unscheduled bleeding, which was also the most common reason for discontinuation (5/18 women). None of the 15 women who had a trans-vaginal ultrasound examination had an endometrial thickness >5 mm. Of the 41 women who had at least one blood progesterone measurement performed, the median value was 11.3 (range 0.7 to 138) nmol/L. This audit indicates that mP is well tolerated when prescribed as MHT. Although there was no evidence of endometrial hyperplasia, further research is needed to establish the safety of mP for continuous combined MHT use.

Introduction

There are observational data to suggest that micronized progesterone (mP) may be associated with a lower risk of breast cancer than other progestins when used as part of a menopausal hormone therapy (MHT) regimen. [1, 2] Taken continuously with oestrogen the recommended dose is 100mg/day, and cyclically, 200mg/day for 14 days. Purported adverse effects of mP at these doses include somnolence, dizziness, fluid retention, weight gain, break though bleeding, breast discomfort and changes in libido, among others. [3]

mP is not approved by the Australian Therapeutic Goods Administration (TGA). Hence, the only available TGA-approved progestins are synthetic. However, under the TGA Authorised Prescriber Program, individual clinicians can be authorised to prescribe non-TGA approved drugs. In seeking TGA approval to prescribe mP to menopausal women it became apparent that the literature pertaining to its use is scant, with no studies reporting the clinical effects of mP 100mg as part as continuous combined MHT. Therefore, 2 years after gaining TGA approval to prescribe mP, an audit of the women treated by an endocrinologist (X) was undertaken to evaluate persistence of use, potentially associated adverse events and reasons for discontinuation. The findings from this audit are presented here.

Methods

The prescribing of mP (Utrogestan®), imported by Lawley Pharmaceuticals, WA) by X commenced in June 2012. From that time on, women commencing or reviewing their MHT were offered the option of mP. In December 2014 the clinical files of all women prescribed mP were reviewed (this was the census date for duration of use for those with on-going treatment). Information extracted from practice records included age, menopausal status, prior estrogen use, concurrent TGA- approved estrogen use, documented adverse events following commencement of mP and the findings of trans-vaginal ultrasound (TVU), when performed in the course of routine care (for example follow up of unscheduled bleeding).Progesterone levels were measured in a number of women selected at random to ensure absorption and in some instances as part of a hormone panel ordered by the general practitioner. These measures were performed by several different commercial pathology laboratories. Women were classified as continuing on mP therapy, having discontinued mP therapy (and the reason for discontinuation), as well as being lost to follow-up (not seen again following the initial prescription of mP). Results are presented as frequencies and proportions as well as in graphical format. The audit was approved by the Monash University Human Research Ethics Committee (CF13/2175-2013001123)and the Cabrini Human Research Ethics Committee (08-05-08-13). No external funding was provided for the audit or the analysis.

Results

During the follow up period 99 women were prescribed mP. Ninety-three of these were postmenopausal when they commenced mP. The six premenopausal women were aged 43 to 50 years at commencement. By December 2014, 2 premenopausal women were lost to follow-up, 2 had ceased mP. One ceased treatment as a result of migraine headache and mood change and the other because of a bleeding and mood change.

Further analysis was restricted to the 93 postmenopausal women. Their mean age at commencement was 55.0 (SD 6.6) years with a range of 33 to 76 years. Their documented mean age at menopause was 48.9 (SD 6.0) years, with a median age of 51 years (range 12 to 58 years). The woman aged 12 years at menopause had Turner Syndrome. The next youngest age at menopause was 32 years. Eleven women had menopause before the age of 45 years, including 5 who had primary ovarian insufficiency (aged < 40 at menopause). By December 2014, 7 women were lost to follow-up, 18

had discontinued mP and treatment was ongoing for 68 women. All postmenopausal women were on continuous combined regimens.

The mean treatment durations for the 68 women continuing mP and for the18 women who ceased mP were 1.7 (SD 0.5) years with a range of 0.4 to 2.5 years and 0.6 (SD 0.6) years with a range from 0.06 to 2.0 years, respectively.

The estrogen therapy prescribed before and after commencing mP is shown in Table 1. The type of concurrent estrogen used by women who continued mP and those ceased is similar, with most using transdermal estrogen. 63% in the ongoing treatment group and 50% of those who ceased were either commenced or changed to transdermal estrogen at the time of commencing mP. The dose of mP was not adjusted according to the estrogen dose as all women were receiving 'standard dose' estrogen therapy approximately equivalent to, or less than, a 50 microgram estradiol patch.

Documented adverse events during mP therapy for the 18 women who ceased treatment and the 68 ongoing are presented in Table 2. The main reasons for stopping mP were bleeding (n=5, including one woman who reported missing tablets) and a combination of bloating, headache and mood change (n=3). Other reasons for cessation (one woman for each reason) included weight gain, unrelated serious illness, mood change, hysterectomy, persistent vasomotor symptoms, switch to herbal therapy, to wean off compounded oestrogen, inconvenience of a daily tablet, breast soreness and none specified. Three women who reported unscheduled vaginal bleeding and ceased mP had changed their estrogen therapy when they commenced mP, as did the two women in the ongoing mP group who also reported bleeding.

None of the 15 women who had a TVU had a double endometrial thickness greater than 5mm. 41 women had at least one progesterone level measured. Progesterone levels were available for 41 women. The levels were done on average 0.46 (range 0 to 1.53) years from commencement of mP and were measured by different laboratories. The average progesterone level was 22.3 nmol/L and the median 11.3 nmol/L (range 0.7-138). The difference is explained by some low and high outlying levels.

Discussion

In this clinical practice audit, nearly three-quarters of the postmenopausal women prescribed mP were continuing to use mP in combination with oestrogen at the audit census date, indicating that

mP was generally well tolerated. The main reasons for mP cessation were as would be expected for any continuous-combined MHT regimen. Of note, nearly one third of the women who ceased therapy did so for unrelated reasons. The number of women lost to follow-up was small. There is a suggestion that the group lost to follow up included an over-representation of women who had previously used compounded hormone therapy.

The blood progesterone levels, although measured in different laboratories, and not timed to dosing, show wide variation in levels, with the very low levels calling to question adherence and the high levels reflecting variation in bioavailability. The absorption of mP following a meal has been reported to be as much as 4 times greater than when mP is taken in a fasted state [4].

Observational data suggests that mP may be the preferred progestin for MHT with respect to breast safety [1]. Although widely used in continuous combined regimens, studies of the protective effects of mP, with respect to the endometrium, are limited to its use in cyclical regimens. In the Postmenopausal Estrogen/Progestin Interventions (PEPI) study [5], conjugated equine oestrogens (CEE, 0.625 mg) plus mP (200 mg/day for 12 days per month) was compared with placebo. After 3 years, there were no significant differences in the occurrence of abnormal endometrial samples in women treated with mP versus placebo. Another endometrial safety study compared cyproterone acetate, 10mg/day with oral mP 200mg/day, cycle day 10-24, in women also receiving percutaneous oestradiol 1.5 mg/day, cycle day 1 to 24 over 18 months.[6] Endometrial biopsies were performed before treatment and between day 18 and day 24 in the last month. 124 women in the cyproterone acetate group and 120 in the mP group had data for analysis. Insufficient sampling occurred in 33.9% of the cyproterone acetate treated group and 60% of the mP group, probably reflecting endometrial atrophy. No case of hyperplasia was reported. The endometrium was atrophic in 27.1%, proliferative in 8.3% and secretory in 62.5% of the evaluable samples from women treated with mP. There are no endometrial sampling studies for continuous combined oestrogen with mP. A study of 30 women over 4 months looked at the endometrial effects of 50, 100mg or 200mg per day of mP combined with 2 mg micronized 17 beta-oestradiol for 25 days each month. Nine of the ten women treated with 100mg mP and all ten women treated with 200mg/day mP had an atrophic endometrium at 4 months.[7]

In a large observational study, Fournier and others reported the use of oestrogen plus mP was associated with an increased risk of endometrial cancer, that increased with duration of MHT use.[8] The degree to which this reflects noncompliance of women having to take two separate medications, as opposed to their oestrogen and progestin in a single tablet or patch is not known.

Our audit demonstrates that mP, at a dose of 100mg/day is well tolerated as part of a MHT regimen. Of note, none of the women treated reported dizziness, somnolence or loss of libido as side effects. It does not provide data for endometrial safety. An appropriately powered endometrial safety study of oral mP, with varying doses of concurrent oestrogen therapy is needed if mP is to be recommended for continuous combined MHT regimens. Until such data is available, whether a dose of oral mP of 100mg daily provides complete endometrial protection remains uncertain.

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7 Darj E, Nilsson S, Axelsson O, Hellberg D. Clinical and endometrial effects of oestradiol and progesterone in post-menopausal women. Maturitas. 1991; **13**: 109-15.

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Table 1. Oestrogen therapy prior to and after commencing micronized progesterone regimen

	Prior oestrogen therapy			Oestrogen therapy prescribed with micronized progesterone		
	Lost to follow up	Ceased U	Continuing U	Lost to follow up	Ceased U	Continuing U
Oestradiol patch		3 (16%)	14 (21%)	4 (57%)	10 (55%)	43 (63%)
Oestradiol gel		1 (6%)	5 (7%)	2 (29%)	3 (17%)	15 (22%)
Oral estrogen	1 (14%)	5 (27%)	9 (13%)	1 (14%)	2 (11%)	6 (9%)
Oestradiol implant		1 (6%)	0		1 (6%)	3 (4%)
Compounded oestrogen	3 (43%)	1 (6%)	3 (4%)		1 (6%)	
Oral contraceptive pill	1 (14%)	1 (6%)	4 (6%)			
Tibolone		5 (27%)	10 (15%)			
Non-hormonal complementary therapy		1 (6%)	0			
Vaginal oestrogen only			1 (2%)			
Had tried many options			1 (2%)			

None	2 (28%)	0	21 (31%)		1 (6%)	1 (1%)
Total	7	18	68	7	18	68

Table 2 Adverse events associated with progesterone therapy

	Ceased* n=18 n(%)	Ongoing[#] n=68 n(%)
Unscheduled bleeding	6 (33.3)	2 (2.9)
Breast symptoms	3 (16.7)	
Fluid retention / bloating	4 (22.2)	1 (1.5)
Headache / migraine	2 (11.1)	
Weight gain	2 (11.1)	1 (1.5)
Mood change	1 (5.5)	
Nausea		1 (1.5)
Tiredness		1 (1.5)
Number of women with no adverse events	5 (27.8)	63 (92.6)

*9 reported one SE, 3 reported 2 and 1 reported 3

[#] 4 reported one SE and 1 woman reported 2 side effects