Micronised progesterone

as a component of menopausal hormone therapy

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Micronised progesterone (mP) was TGA approved in 2016 for use as a progestogen in menopausal hormone therapy (MHT). It has improved bioavailability when taken orally, appears to have a more favourable breast safety profile than other progestogens, is neutral with respect to cardiovascular disease risk and does not cause adverse mood effects.

The primary use of menopausal hormone therapy (MHT) is to alleviate symptoms of oestrogen deficiency, such as hot flushes, night sweats, sleep disturbance, arthralgia and vulvovaginal atrophy symptoms.[1] Co-prescription of a progestogen is essential with oestrogen therapy for perimenopausal or postmenopausal women with an intact uterus to protect against endometrial hyperplasia and the possibility of endometrial carcinoma. The progestogen is usually administered cyclically for 14 days per month up until 12 months after the final menstrual period, resulting in cyclical menstrual loss. After that, the progestogen may be taken continuously, such that menstrual bleeding does not occur.

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Micronised progesterone (mP) has been available in Europe and the USA for several decades as a progestogen option for the management of women with menopausal symptoms. In Australia, mP was approved by the TGA in June 2016 for use in MHT, as well as to treat women with menstrual abnormalities or secondary normogonadotrophic amenorrhoea. Of note, this approval applies to the specific mP formulation Prometrium and does not represent generic approval of compounded progesterone formulations. This article discusses the use of mP as a component of MHT.

What is micronised progesterone?

Progestogens include progesterone and synthetic progestins. Progesterone is the main hormone produced by the corpus luteum in the luteal phase of the menstrual cycle and by the placenta. In the luteal phase, progesterone converts the functional endometrium from being proliferative to secretory. Progesterone has poor bioavailability when taken orally unless it has been micronised. Micronisation is a process by which the average particle diameter of the progesterone is reduced to the micrometre range, which facilitates absorption by the gut. After oral administration, mP exhibits all the properties of endogenous progesterone, with induction of a secretory endometrium when given cyclically with oestrogen.[2] Like endogenous progesterone, mP has slightly anti-aldosteroneric effects. Micronised progesterone has been used extensively in Europe since 1980 and was made available for use in the USA in 1998.

Why use micronised progesterone?

Progestogens differ in their binding to various steroid receptors, resulting in different clinical profiles.[3] All are progestogenic, but some such as norethisterone are more androgenic, whereas others such as medroxyprogesterone acetate (MPA) bind to the glucocorticoid receptor, potentially causing symptoms of glucocorticoid excess at high doses. Progesterone, drospirenone and to a lesser extent dydrogesterone exhibit antimineralocorticoid effects.

TABLE. CONTRAINDICATIONS TO USE OF MICRONISED PROGESTERONE AS PART OF MENOPAUSAL HORMONE THERAPY

TGA listed contraindication	Comment
Undiagnosed postmenopausal vaginal bleeding	Requires investigation
Known allergy or hypersensitivity to progesterone or to any of the excipients	Capsules contain sunflower oil, soya lecithin, gelatin, glycerol and titanium dioxide as well as mP
Severe hepatic dysfunction	Micronised progesterone requires hepatic metabolism
Breast or genital tract cancer	Progestins, including mP, may be prescribed after endometrial or cervical cancer
Thromboembolic disease	No evidence that mP influences venous thromboembolic events
Thrombophlebitis	No evidence that mP influences venous thrombophlebitis
Cerebral haemorrhage	No evidence to implicate progesterone in cerebral haemorrhage
Porphyria	–

Abbreviation: mP = micronised progesterone.

Micronised progesterone does not influence blood pressure in normotensive postmenopausal women but results in a dose-dependent fall in blood pressure in women with hypertension and counteracts the increase in blood pressure that is sometimes seen with oral oestrogen therapy.[4] When combined with oestrogen, mP does not interfere with the favourable cardiovascular effects of oestrogen, in contrast to MPA, which antagonises the protective effects of oestrogens.[5] Unlike some of the norpregnane progestins, mP is not prothrombotic.[6]

Large observational studies indicate that mP may be the preferred progestogen for MHT with respect to breast safety.[7] In support of this, mP 100 mg/day combined with transdermal oestradiol for eight weeks did not increase breast cell proliferation markers, whereas an increase in breast cell proliferation was seen with MPA.[8] Clinical trials have demonstrated endometrial safety with this formulation of mP when used both cyclically and for 25 days per month.[2,9,10]

How is micronised progesterone used?

For cyclical MHT, mP should usually be prescribed at a dose of 200 mg/day for 14 days each month to ensure endometrial protection. For convenience, a calendar month is used, such that women take oestrogen therapy continuously, and mP from days 1 to 14 of each calendar month. This usually results in a cyclical bleed. When a woman is at least 12 months past the menopause, mP can be prescribed continuously, although most studies have reported on the use of mP for 25 days per month. Of note, these studies have used standard-dose oestrogen therapy, such as conjugated equine oestrogen 0.625 mg/day.[2] There are no available data on the dose of mP required for endometrial protection when high-dose oestrogen therapy is used. The *Practitioner's Toolkit for Managing the Menopause*, which has been widely endorsed, provides dosage guidance for all currently available oestrogen and progestogen preparations (available online at: http://www.tandfonline.com/doi/full/10.3109/13697137.2014.929651).[11]

Side effects

Suggested side effects of mP at standard doses include somnolence, dizziness, fluid retention, weight gain, breakthrough bleeding, breast discomfort and changes in libido.[12] It is therefore suggested that mP be taken at night to avoid daytime sleepiness. In our clinical audit of 93 postmenopausal women treated with mP, 68 women (73%) had no side effects.[13] The potential side effects reported, with some women having several, included unscheduled bleeding (n=8), fluid retention or bloating (n=5), breast symptoms (n=3), weight gain (n=3), headache (n=2) and mood change (n=1). Somnolence was reported by one woman. Thus, mP is extremely well tolerated. If systemic side effects do occur then women can administer the mP capsule as a vaginal pessary, which may ameliorate the reported side effect.

Precautions

Before commencing any MHT, and at regular intervals thereafter, every woman should undergo assessment. A personal and family medical history should be taken, and physical examination and investigations should be guided by the findings.

Contraindications to mP as part of MHT are listed in the Table. Evidence to implicate mP in thromboembolic events, thrombophlebitis and cerebral haemorrhage is lacking, although these are considered general contraindications to MHT.

Data from randomised clinical trials support a protective effect of mP on the endometrium when administered cyclically and for 25 days per month. However, a large observational study reported that oestrogen plus mP was associated with an increase in the risk of endometrial cancer, which increased with duration of use.[14] The significance of this finding has been questioned by experts in the field for a range

of reasons. First, the finding was based on only 26 cases of endometrial cancer. Secondly, MHT use was documented only at baseline, yet the findings pertain to a nine-year follow-up period, during which time MHT use was not assessed, and the MHT regimens at baseline were not specified.[15] Furthermore, the extent to which the finding reflects noncompliance of women taking two separate medications rather than oestrogen and progestogen in a single tablet or patch is not known. Our recent clinical audit of women in Australia treated with continuous mP as part of MHT did not raise concerns.[13] As for any MHT regimen, any unscheduled vaginal bleeding occurring three months after initiating therapy requires formal investigation.

Conclusion

Micronised progesterone is an effective, well-tolerated progestogen for use either cyclically or continuously as part of MHT. It appears to have a more favourable breast safety profile than other progestogens, is neutral with respect to cardiovascular disease risk and does not cause adverse mood effects. Although only recently approved in Australia, mP has been available in Europe and the USA for several decades for the management of women with menopausal symptoms, and continues to be considered a first-line progestogen in this context. MT

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