Long-term menopausal treatment using an ultra-high dosage of tibolone in an elderly Chinese patient – Case report

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ABSTRACT

This report describes the special case of a Chinese woman with severe vasomotor symptoms (VSMs), depressed mood, low energy and genitourinary syndrome of menopause, including problems of sexual dysfunction, who was treated with tibolone. The aim of the report is to highlight the value of individualizing menopausal hormone therapy (MHT) type and dosage. Since 16 years of previous treatment with various other forms of MHT had not provided satisfactory efficacy in this patient, at the age of 71 years she was prescribed tibolone, starting at the usual lowest dosage of 1.25 mg/day. We gradually had to increase the dosage of tibolone up to 7.5 mg/day, which is three-fold the recommended maximum dosage. We added three-monthly sequential dydrogesterone to reduce the risk of breakthrough bleeding and the risk of endometrial cancer. To date, we have observed no side effects and no remarkable abnormal laboratory assessments, with the exception of increased thyroid-stimulating hormone, which we monitor six-monthly. Even though the patient has been informed about potential risks, such as increased risks of stroke, breast cancer and endometrial cancer, as described in the discussion, she has now been willing to accept this ultra-high dosage for seven years, and wishes to continue with this treatment.

KEYWORDS

MHT, ultra-high dosage tibolone, elderly women.

Introduction

Founded ten years ago, our "Menopause Clinic" is the first specialized center of its kind acknowledged by the health authorities of China. We treat more than 500 outpatients every day, of whom about 20–30% require menopausal hormone therapy (MHT). We therefore have huge experience in using the different regimens available in China. Here we report the case of a now 79-year-old woman who suffered from severe menopausal symptoms and genitourinary syndrome of menopause (GSM) and has been treated, over a period of 24 years, with several MHT regimens. Ultimately, only tibolone, 7.5 mg/day (three-fold the officially recommended maximum dosage of this drug) has provided sufficient long-term efficacy.

This aim of this report is to increase awareness of individualized MHT in elderly women, to highlight the limited treatment efficacy observed in special patients using conventional MHT, and to briefly examine the literature on tibolone, with its excellent tolerability, even when using a dose of 7.5 mg/day.

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Case report

History: first symptoms, examinations, diagnosis and use of different MHT regimens

In 1996, a 55-year-old non-smoking female of Han nationality attended the cardiology clinic of another hospital complaining of irritability, chest tightness and shortness of breath, hot flushes (6-12 times/day), and frequent urination (1–2 times/hour). After undergoing an electrocardiogram, cardiac color Doppler ultrasound, myocardial enzyme testing and other related tests, she was informed that there was no abnormality, and advised to see a doctor in a gynaecological department. She thus attended the gynaecological department of another hospital where "menopausal syndrome" was diagnosed. There, she was prescribed nilestriol 2.5 mg every 14 days, sequentially combined with medroxyprogesterone acetate (MPA, 6 mg, q.d. for 10 days every 4 weeks), which she used for eight years despite obtaining insufficient relief of the menopausal symptoms (nilestriol has frequently been used in China, but is rarely used in other countries).

The patient first visited our "Menopause Clinic" in 2004, still with menopausal complaints and GSM, also associated with symptoms such as depressed mood, low energy and sexual dysfunction (libido problems); she had a modified Kupperman score of 30. Her height was 160 cm, weight 60.8 kg, blood pressure 120/82 mmHg, and pulse rate 67/min. Regarding her history, her menarche occurred at age 14, with regular cycles,

menstruation lasting 6–7 days, and cycles 28–30 days. She had four pregnancies (three children, one abortion), and had a natural menopause at age 53, without any other diseases. Comprehensive laboratory and clinical assessments were performed, including sex hormone levels, liver and kidney function, insulin level, pelvic examination, cervical examination (TCT and HPV), transvaginal ultrasound, electrocardiogram, mammography, lumbar bone mineral density (BMD) measured by quantitative computed tomography (QCT), and assessment of muscle function and nutritional metabolism (based on the measurement of static metabolic rate, body composition, quality and quantity of diet, exercise), in order to provide her with individualized nutrition and exercise advice. All the examinations (cardiac, mammary etc.) were within the normal range. Menopause syndrome at postmenopausal stage was diagnosed.

The treatment with nilestriol/MPA was stopped, and over the following eight years different types of MHT and dosages were tried. Thus, the patient received conjugated equine estrogens (CEE) (0.9 mg)/dydrogesterone (10 mg), estradiol (1 mg)/drospirenone (2 mg) (Angeliq®), estradiolvalerate (2 mg)/cyproterone acetate (1 mg) (Climen), and estradiol/dydrogesterone (Femoston®) (1/10, 2/10). However, she continued to report intolerable symptoms and irregular bleeding.

History of tibolone use from normal up to ultra-high dosages

Tibolone was first used in this patient in 2012 (by which time the woman was aged 71 years!). Initially, the lowest dosage of tibolone (1.25 mg/day) was used, which was subsequently increased to 2.5 mg/day; then, because she still was not getting a satisfactory effect, we further increased it up to 5 mg/day, each dosage being tested for at least 6 months. Finally, we decided to treat with an ultra-high dosage of tibolone, 7.5 mg/day, for the first time in 2014.

We have sometimes obtained good results by combining tibolone with a progestogen (10 mg/day, for 14 days every 3 months) to avoid excessive endometrial thickness and breakthrough bleeding; we also used this approach successfully in this patient. Indeed, all bleeding stopped with this combined treatment regimen. Even though the patient has been informed about known increased risks (of stroke, breast cancer and endometrial cancer, for example) associated with the use of tibolone, she still wants to continue with this therapy. Hence, her present treatment is tibolone (7.5 mg/day) and dydrogesterone (10 mg, q.d. for 10 days every 3 months). Promestriene vaginal capsules (10mg/night, q.d., external use) were prescribed to enhance the treatment effect on vaginal complaints, and calcitriol capsules (0.25 mg/day, q.d.) to optimize the prevention of osteoporosis. Furthermore, we advised the patient to implement postmenopausal lifestyle changes, i.e., our routine programme for overweight postmenopausal women, including individualized diet, exercise and lifestyle guidance after professional auxiliary examinations.

Current clinical situation

Clinical examination (September 2020) revealed overweight (height: 160 cm, weight: 66 kg, BMI 25.78 kg/m^2, waistline: 100 cm, hipline: 107 cm). Pelvic examination showed postmenopausal changes, and no other abnormalities. Her uterus was 5.7*5.3*5.2 cm, with a 2.6 cm uterine fibroid in the anterior wall, endometrial thickness 0.6 cm. Hormone characteristics (during tibolone) (November 16, 2019): follicle-stimulating hormone: 30.38 IU/L, luteinizing hormone: 16.16 IU/L, estradiol: <11.8 pg/ml, progesterone: 0.37 ng/ml, prolactin: 12.0 ng/ml, and testosterone: 23.71ng/dl.

The results of liver, kidney function and other laboratory analyses are shown in Table 1. Plasma levels of fasting insulin and cortisol were within the normal range. Although thyroid-stimulating hormone (TSH) was slightly above normal, free thyroglobulin 3 (fT3), free thyroglobulin 4 (fT4), and other thyroid indexes were normal; we also assessed fT3 and fT4 every 6 months to check for "sub-clinical hypothyroidism".

Table 1 Levels of liver and kidney function, blood glucose and lipids and other laboratory results (November 16, 2019).

	Results	Reference range
ALT (IU/L)	28.6	5.00-40.00
AST (IU/L)	24.3	5.00-40.00
LDH (IU/L)	179	109.00-245.00
BUN (mmol/L)	4.00	1.60-8.30
Cr (umol/L)	55.6	45.00-106.00
INS (pmol/L)	52.86	21.00-174.00
GLU (mmol/L)	5.02	3.90-6.10
CHO (mmol/L)	4.25	0.00-5.20
TG (mmol/L)	0.69	0.00-1.70
HDL (mmol/L)	1.08	1.04-1.60
LDL (mmol/L)	2.69	2.07-3.37
Apo-A1 (g/L)	1.26	1.20-1.60
Apo-B (g/L)	0.85	0.60-1.10
TSH (mIU/L)	5.56	0.55-4.78
T3 (nmol/L)	1.74	0.92-2.79
T4 (nmol/L)	79.90	58.10-140.60
FT3 (pmol/L)	4.25	3.50-6.50
FT4 (pmol/L)	12.38	11.50-22.70
aTG (U/ml)	17.70	0.00-60.00
aTPO (U/ml)	33.70	0.00--60.00
COR (nmol/L)	589.71	118.60-618.00
CRP (mg/L)	0.85	0.00-10.00
REE (Kcal/d)	1829	1224
BMD (mg/cm^3)	276.9	>120

*Abbreviations: **ALT**, alanine aminotransferase; **AST**, glutamic-pyruvic transaminase; **LDH**, lactate dehydrogenase; **BUN**, urea nitrogen; **Cr**, creatinine; **INS**, insulin; **GLU**, glucose; **CHO**, cholesterol; **TG**, triglycerides; **HDL**, high-density lipoprotein; **LDL**, low-density lipoprotein; **Apo-A1**, apolipoprotein A1; **Apo-B**, apolipoprotein B; **TSH**: thyroid-stimulating hormone; **T3**: total thyroglobulin 3; **T4**: total thyroglobulin 4; **FT3**: free thyroglobulin 3; **FT4**: free thyroglobulin 4; **aTG**: anti-thyroglobulin antibody; **aTPO**: anti-thyroid peroxidase antibody; **COR**: cortisol; **CRP**: C-reactive protein; **REE**: energy expenditure at rest; **BMD**: bone mineral density.*

QCT (November 19, 2019) showed a lumbar BMD of 276.9 mg/cm^3; because this was higher than 120 mg/cm^3, it was diagnosed as normal. With regard to breast imaging, bilateral mammograms (November 19, 2019) showed BI-RADS grade 2 and bilateral breast hyperplasia, which are considered benign changes; regular follow up is recommended. The patient's energy expenditure at rest, reflecting energy metabolism in the basic state, was 1.829 kcal/d, which is higher than reference value (1.224 kcal/d). On the basis of the clinical manifestations and history, the patient's diagnosis was menopausal syndrome, postmenopausal endometrial thickening and myoma of the uterus.

During treatment (tibolone 7.5 mg from 2014 to now), the frequency of daytime VMS episodes decreased from 6/day on average to 1–2/day, while night sweats decreased from 2–4/night to 2/night. Hot flush/night sweat intensity also significantly decreased. Urinary frequency also decreased, from 2–6 times/h to 2 times/day. Table 2 shows the excellent efficacy of ultra-high dose tibolone according to the modified Kupperman score.

Discussion

The decision to use tibolone was based primarily on the insufficient efficacy obtained using various conventional MHT regimens during eight years. Furthermore, because the patient also had depressed mood, low energy, libido problems etc., we wanted some androgenic effects. We opted for tibolone because we have very good experience with it in these women, even though we are well aware that tibolone is not recommended in elderly women particularly, because of the increased risk of stroke.

Tibolone is a synthetic steroid hormone which has strong estrogenic and weak progestogenic activities, as well as some androgenic properties [1]. Tibolone is approved in 90 countries for treatment of climacteric symptoms in postmenopausal patients and in 55 countries for the prevention of osteoporosis. Tibolone should not be used in elderly women and women who have risk factors for stroke, such as hypertension, smoking, diabetes and atrial fibrillation [2]. The usual lowest dosage is 1.25 mg/day, which is often the starting dosage in China; while the optimum dose for obtaining relief of severe VMS [2] and treatment of osteoporosis [3] is 2.5mg/day. Thus, the three-fold higher dosage in our report can certainly raise concerns over the risks known from clinical studies, especially in older women.

The main concern with every MHT is the risk of breast cancer. Tibolone increased the risk of recurrence in breast cancer patients [4], while in healthy postmenopausal women tibolone caused less stimulation of breast tissue than conventional MHT, as judged by mammographic breast density and fine-needle aspiration studies [5]. The most likely explanation is that tibolone exerts an estrogenic effect on occult, dormant breast-cancer metastasis [6]. Tibolone increased the absolute risk of stroke by 2.3 (95% CI, 0.4 to 4.2) per 1000 person-years and increased the relative hazard risk by 2.19 (95% CI, 1.14 to 4.23) [4]. However, there was a decreased risk of colon cancer using tibolone [7]. Tibolone can induce endometrial proliferation and might increase the risk of endometrial cancer [8], even though the absolute risk was small during 3 years of therapy [2]. Although the issue of endometrial cancer risk is controversial, in general addition of a progestogen to tibolone is not recommended. However, we are cautious and add progestogen (10mg/day for 14 days) at regular, 3 months intervals, especially if tibolone is used at higher dosages. As for the type of progestogen, we have good experience using dydrogesterone which is neutral in the cardiovascular/metabolic system and may also have a lower

Table 2 Modified Kupperman score (September 1, 2020).

Symptoms	Basic score	Degree score			
		0	1	2	3
VMS	4	None	<3 times/day(✓)	3-9 times/day	≥10 times/day
Sensory disturbance	2	None (✓)	Sometimes	Often	Often and serious
Insomia	2	None (✓)	Sometimes	Often	Often and serious, needs medication
Depression	2	None (✓)	Sometimes	Often, can control	Loss of confidence in life
Anxiety	1	None (✓)	Sometimes	Often, it does not affect work and life	Often, can't control oneself
Dizziness	1	None (✓)	Sometimes	Often	Influences life and study
Fatigue	1	None	Sometimes (✓)	Often, it doesn't affect function	Limits daily activities
Pain in muscles and joints	1	None	Sometimes (✓)	Often, tolerable	Dysfunction
Headache	1	None(✓)	Sometimes	Often, it does not affect work and life	
Palpitations	1	None	Sometimes (✓)	Often, tolerable	Needs medication
Formication	1	None (✓)	Sometimes		Needs medication
Sexual life	2	Normal (✓)	hyposexuality	Sexual difficulties	Loss of sexual desire
Symptoms of urinary irritation	2	None	Occasionally (✓)	≤3 times/year, self-healing	>3 times/year, need medication

Note: Basic score means weighted score for each symptom. A score of >30 is severe, 16-30 is moderate, and < 6-15 is mild,0-5 is normal.

risk of breast cancer. Compared to progesterone, dydrogesterone certainly has stronger endometrial efficacy (lower frequency of bleeding problems).

Tibolone can decrease HDL-cholesterol, which we did not see in our patient, but can improve lipoprotein(a) and increase plasminogen levels, which may both lead to a decreased risk of venous thrombosis, although this risk is still controversial [2,9]. Treatment with tibolone had no effect on blood pressure or fasting blood glucose levels [10]. In our laboratory assessments all values were within the normal range with the exception of an increased TSH value (Table 2). Because our patient has no symptoms of hypothyroidism, we recommended monitoring of all thyroid function parameters every 6 months.

Conclusion

The choice of the type and dose of MHT should be individualized, with patients closely monitored during treatment. Here we report the case of an elderly patient with menopausal symptoms and persistent GSM treated with different types of MHT over a period of 24 years. During the first eight years, treatment with nilestriol, performed in another gynecological department, was not sufficiently effective, which was probably to be expected, given that this is a derivative of 17alpha-ethinylestradiol, which is much less effective than CEE or estradiol. However, even using these latter estrogens, treatment over the following eight years was still not satisfactory, until we changed to tibolone, starting at 1.25 mg/day and increasing the dosage gradually to the present ultra-high dosage of 7.5 mg/day. The good tolerability may be related to ethnic background, an aspect that should be considered when interpreting our case.

For many reasons the "gold standard" in MHT is currently transdermal estradiol combined with progesterone or dydrogesterone. However, for individualized therapy we should not forget that we have still other options like tibolone, already in use for decades, with its special androgenic properties offering advantages for patients with symptoms like low energy, depressive mood, libido problems, etc. As seen in our case, tibolone can even be well tolerated in ultra-high dosages, which, however, should be used only in exceptional cases and if other therapies have been found to be ineffective or less effective.

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