Alleviation of the Climacteric Symptoms with Oral Sequential Hormone Replacement Therapy

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Abstract

The efficacy of the oral hormone replacement therapy (HRT) preparation estradiol valerate/levonorgestrel (EV/LNG, Klimonorm®) in the alleviation of the menopausal complaints of peri- and postmenopausal Thai women was studied in a prospective, open, uncontrolled phase IV clinical trial. Of the 50 peri- or postmenopausal women screened, 39 completed the study. From them 31 were postmenopausal and 8 perimenopausal. The participants received EV/LNG over a period of 6 cycles. The Menopause Rating Scale II (MRS II) was used to assess the effect of EV/LNG on the menopausal symptoms.

The changes in the main parameters of the MRS II during the treatment with EV/LNG showed that the general score decreased by 34.9 per cent after 3 months and was kept at the same value after 6 months of treatment. The somato-vegetative complaints decreased by 32.5 per cent after 3 months and by 35 per cent after 6 months. The psychological complaints decreased by 34.1 per cent after 3 months and by 32.9 per cent after 6 months. The urogenital complaints decreased by 29.3 per cent after 3 months, and remained at the same level after 6 months of treatment. In conclusion, the 6-months administration of the oral HRT preparation estradiol valerate/levonorgestrel caused a considerable alleviation of the climacteric symptoms in menopausal women.

Key word : Climacteric Symptoms, Menopause, Hormone Replacement Therapy, Estradiol Valerate/Levonorgestrel

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Hormone replacement therapy (HRT) has become the standard for the treatment of menopausal complaints[1]. The benefits of HRT include relief of vasomotor symptoms, improvement of mood and sleep disturbances, treatment of symptoms resulting from postmenopausal urogenital atrophy, reduction of the risks of osteoporosis, and Alzheimer's disease. To date only estrogen could treat effectively all menopausal symptoms. However unopposed estrogen substitution may cause hyperplasia of the endometrium, which increases the risk of endometrial cancer[2]. To reduce the development of endometrial hyperplasia, the continuous or cyclic addition of a progestogen is necessary in women with an intact uterus[2,3]. The use of a combined estrogen/progestogen regimen is designated as combined HRT. The estrogenic component of an HRT drug is usually estradiol valerate (EV). The selection of a suitable progestogen is very important in the development of a combined HRT preparation[4]. Due to its strong progestational effect on the endometrium, and its antiestrogenic effect, levonorgestrel (LNG) is very effective in suppression of the estrogen-induced endometrial proliferation[4,5].

The evaluation of menopausal complaints is done mainly by the use of the Kupperman index[6]. The Menopause Rating Scale II (MRS II) was developed recently as a modern tool for the assessment of menopausal complaints[7]. Subsequent investigations have shown the reliability of this self-administrative scale[8-11].

The aim of this study was to investigate the efficacy of an oral HRT drug containing estradiol valerate and levonorgestrel in the treatment of the menopausal symptoms in peri- and postmenopausal Thai women.

MATERIAL AND METHOD

Drug

Estradiol valerate/levonorgestrel (EV/LNG, Klimonorm®, Jenapharm GmbH & Co. KG, Jena, Germany) is a sequential oral estrogen-progestogen hormone replacement drug[12]. EV/LNG contains 2 mg EV during the first phase (9 days) and 2 mg EV plus 0.15 mg LNG during the second phase (12 days). A 7-day drug-free interval follows prior to starting the next treatment cycle.

Study design

The study was a prospective, open, uncontrolled phase IV clinical trial, carried out in the menopause clinic, Ramathibodi Hospital, Bangkok on outpatient women. Of the 50 peri- or postmenopausal women screened, 47 fulfilled the inclusion and exclusion criteria, 6 did not begin taking the drug, and 2 terminated the study prematurely because of occurrence of adverse effects. Thus, 39 women completed the study. Of those 31 were postmenopausal and 8 perimenopausal. All participants were fully informed about the purpose of the study and gave their voluntary consent to participate in it. They received Klimonorm® over a period of 6 cycles. The general parameters of the study participants are presented in Table 1, Fig. 1 and 2.

The Menopause Rating Scale II (MRS II) [7] was used to assess the effect of EV/LNG on the menopausal complaints. The following symptoms were recorded: hot flushes and sweats (sudden appearance of feeling hot and/or sweating), heart complaints (palpitations, tachycardia, extrasystoles, nervous heart trouble), sleep disturbances (problems in falling asleep or sleeping through, premature awakening, sleeplessness), joint and muscle complaints (aching joints

Table 1. General parameters of the subjects included in the study.

Parameter	N	Mean ± SD
Age (years)	39	52.3 ± 3.6
Height (cm)	39	154.2 ± 4.3
Weight (kg)	39	56.9 ± 6.0
BMI (kg/m^2)	39	23.4 ± 2.5
Systolic blood pressure (mmHg)	39	123.3 ± 12.2
Diastolic blood pressure (mmHg)	39	77.7 ± 8.7
Menarche (years)	39	14.5 ± 1.6
Perimenopause (months)	8	7.1 ± 1.7
Postmenopause (months)	31	44.0 ± 34.5

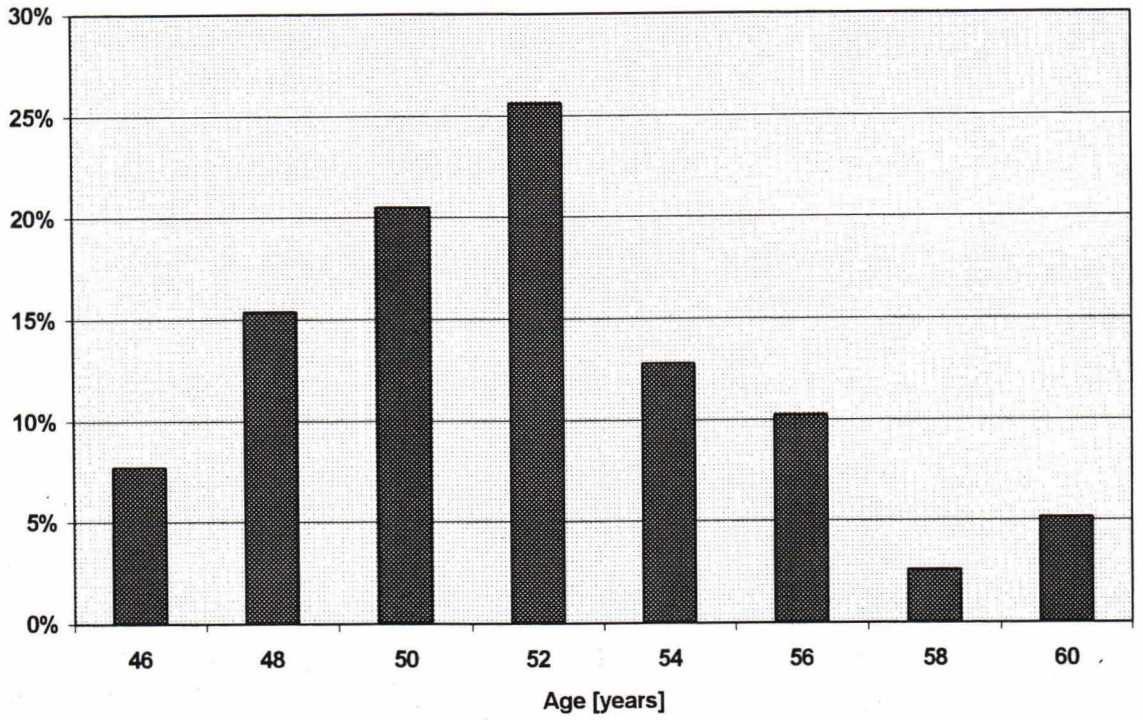

Fig. 1. Distribution of age.

and/or muscles, rheumatoid complaints), depressive moods (despondency, sadness, feeling lachrymose, lack of motivation, sudden and/or frequent mood swings), irritability (nervousness, tension, aggression), anxiety (restlessness, panic), physical/mental exhaustion (general reduction in performance, reduced memory, lack of concentration, forgetfulness), sexual problems (changes in sexual desire, sexual habits and satisfaction), urinary tract complaints (urination complaints, urinary urgency, urinary incontinence), and vaginal dryness (feeling of vaginal dryness and soreness, pain during sexual intercourse).

Separate processing of the results was made for the following subscales: general score (all listed symptoms); somato-vegetative complaints (hot flushes, sweats, heart complaints, sleep disturbances, joint and muscle complaints); psychological complaints (depressive moods, irritability, anxiety, physical/mental exhaustion), and urogenital complaints (sexual problems, urinary tract complaints, vaginal dryness).

Statistical evaluation

Data obtained in the collected questionnaires were transferred to Access 97 spreadsheets. By means of this program package, analysis was done descriptively and exploratively. The results were presented as means ± SD. Only in some cases calculations were made for statistical significance between the baseline values and the end of the observational period.

RESULTS

The changes in the main parameters of the Menopause Rating Scale II during the treatment with EV/LNG are presented in Table 2. The general score decreased from the initial values of 18.9 to 12.3 (by 34.9%) after 3 months and was kept at the same value after 6 months of treatment. The somato-vegetative complaints decreased from the mean values of 4.0 to 2.7 (by 32.5%) after 3 months and to 2.6 (by 35%) after 6 months. The psychological complaints decreased from the mean value of 8.2 to 5.4 (by 34.1%) after 3 months and to 5.5 (by 32.9%) after 6 months. The urogenital complaints decreased from 5.8 to 4.1 (by 29.3%) after 3 months, and remained at the same level after 6 months of treatment. The changes of the single parameters studied are shown in Table 2. It could be seen that most pronounced improvement was achieved in the vaginal dryness (57.9%), followed by joint and

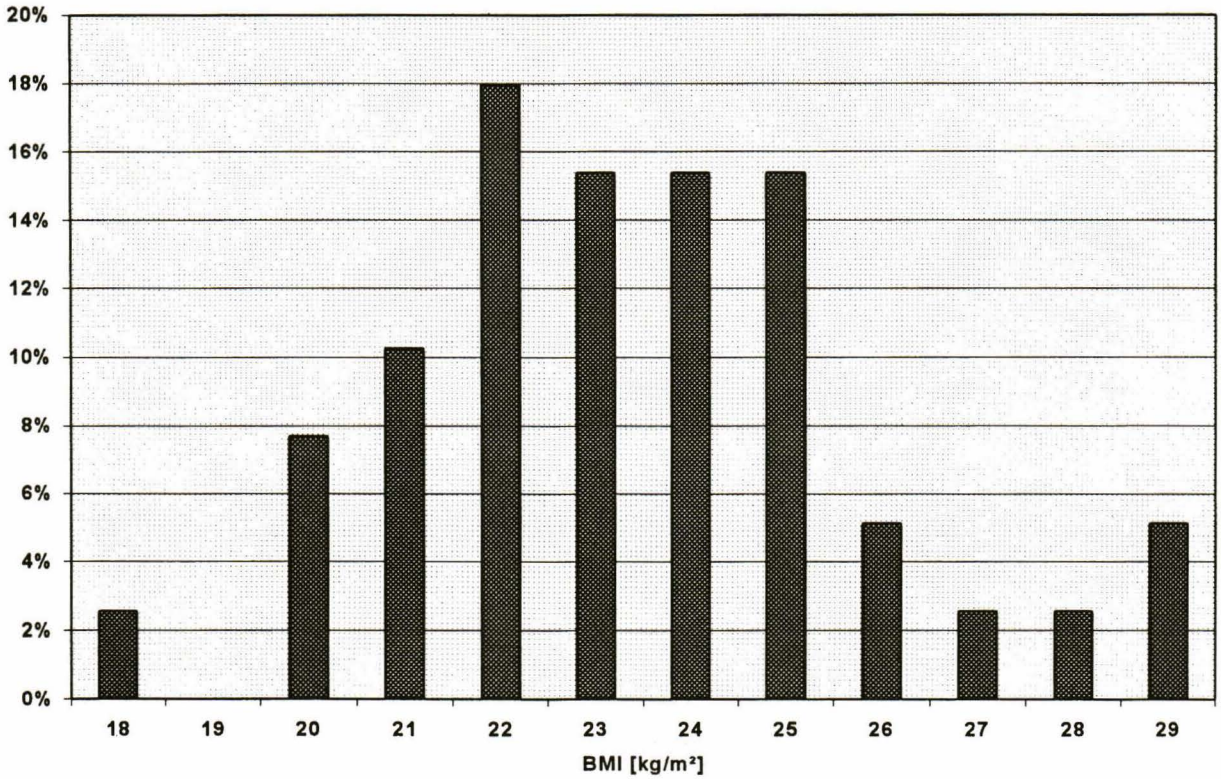

Fig. 2. Body mass index.

muscle complaints (56.8%), anxiety (47.4%), sleep disturbances (44.5%), depressive moods (43.2%), and hot flushes and sweats/irritability (42.1%). Most unchanged were the parameters of heart complaints (60.5%), followed by sexual problems/irritability (47.4%), and depressive moods (46.0%).

The body weight gain was not found during the study period in the Thai women. Their weight remained rather constant.

DISCUSSION

The effect of the oral sequential estrogen-progestogen HRT preparation EV/LNG (Klimonorm®) in relieving climacteric symptoms was well documented in the present study. The present study showed a decrease of MRS II by about 35 per cent, which is close to the results of Rudolph et al[13] who studied the changes in psychic and somatic well-being, self-esteem, and cognitive capabilities of 78 peri- and postmenopausal women after 2 months treatment with EV/LNG in a multicenter, prospective, open-label postmarketing surveillance trial. However, the present study showed that some women reported the unchanged or worsened symtoms after treatment. This finding can be explained that these menopausal symtoms are affected and modified by several factors, so hormone replacement therapy could not alleviate these symptoms in all women. MRS II scores decreased significantly from 22.2 to 12.7 points (by 42.7%). A marked improvement of the Kupperman index (a decrease by 45.9%, $p < 0.05$) after 2 months use was also reported. The authors found a good correlation between the Kupperman index and the MRS II scores.

Several studies have investigated the reliability of MRS II in comparison with the Kupperman index. MRS II was developed in order to improve the assessment of the menopausal complaints by adding more parameters reflecting the quality of life disturbances in menopause. Schneider et al[8] compared the results obtained by the use of MRS II with two other scales: the Kupperman index and SF-36. A

Table 2. Changes in the main parameters of the Menopausal Rating Scale II in the subjects after 6-months treatment with EV/LNG.

Symptoms	Number of subjects showing symptoms	Improved (%)	Unchanged (%)	Worsened (%)
Hot flushes and sweats	38	42.1	44.7	13.2
Heart complaints	38	26.3	60.5	13.2
Sleep disturbances	36	44.5	38.9	16.6
Joint and muscle complaints	37	56.8	18.9	24.3
Depressive moods	37	43.2	46.0	10.8
Irritability	38	42.1	47.4	10.5
Anxiety	38	47.4	42.1	10.5
Physical/mental exhaustion	38	39.5	39.5	21.0
Sexual problems	38	36.8	47.4	15.8
Urinary tract complaints	37	37.8	43.2	19.0
Vaginal dryness	38	57.9	36.8	5.3

population sample of 306 women from a survey completed simultaneously the corresponding questionnaires. A high correlation was found between the scores of the Kupperman index and MRS II ($r = 0.91$). In a similar study the same authors established a high reliability of the MRS scores[9]. MRS has been used successfully in a big postmarketing surveillance study of Climen comprising 10904 pre- and postmenopausal women[10].

Improvement of the menopausal complaints as assessed by the Kupperman index after administration of EV/LNG has been reported in several studies. In a multicenter, randomized, double-blind study on 210 postmenopausal women Gräser et al[14] found a decrease of the Kupperman index (by 71.9% after 3 months, and by 81.6% after 6 months of treatment). In a study on 123 postmenopausal women Burdová et al[15] found a statistically significant ($p < 0.0001$) decrease in the Kupperman index by 69.6 per cent after 6 months and by 93.6 per cent after 9 months. Georgiev et al[16] reported a significant reduction of the severity of the climacteric symptoms of 100 outpatient peri- and postmenopausal women, as assessed by the use of the Kupperman index - from 27.9 to 9.3 points after 3 months (by 66.7%), and to 4.0 points (by 85.7%) after 6 months of treatment with EV/LNG.

The clinical effectiveness of EV/LNG was also demonstrated in the prevention of postmenopausal osteoporosis[17,18], favorable effect of lipid metabolism[14-17], and counteraction of urogenital atrophy[19]. Therapy with EV/LNG resulted in stabilization of the cycle length. Cycles with regular withdrawal bleeding periods lasting 3-4 days were restored in most of the women[14,15,20]. The thickness of the endometrium did not change significantly after a 3-year administration[15]. There were no clinically significant changes in body weight, blood pressure, hematological tests, and other laboratory parameters[11,14,15,18].

In conclusion, the 6-months administration of the oral sequential estrogen-progestogen HRT preparation EV/LNG (Klimonorm®) in Thai peri- and postmenopausal women caused a considerable alleviation of the climacteric symptoms as assessed by the Menopause Rating Scale II (MRS II). The somatovegetative complaints, the psychological complaints, and the urogenital complaints decreased by 30-36 per cent after 3 months, and remained at the same level after 6 months of treatment. The study showed a good correlation of the results obtained by the use of MRS II with that obtained using the Kupperman index in similar studies on EV/LNG.

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การลดลงของอาการวัยหมดประจำเดือนในสตรีวัยหมดประจำเดือนที่ได้รับฮอร์โมนทดแทนที่ประกอบด้วย เอสตราไดออล วาเลอเรต/เลโวนอร์เจสเตรล

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การศึกษาไปข้างหน้าถึงประสิทธิผล ในการรักษาอาการวัยหมดประจำเดือนในสตรีวัยหมดประจำเดือนด้วยฮอร์โมนทดแทนที่ประกอบด้วย estradiol valerate/levonorgestrel โดยทำการศึกษาในสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือนที่มีอาการผิดปกติจำนวน 50 คน ในสตรีจำนวนนี้พบว่า 39 คน ได้เข้าร่วมการศึกษาจนครบ 6 เดือน โดยเป็นสตรีวัยหมดประจำเดือน 31 คน และสตรีวัยใกล้หมดประจำเดือน 8 คน ทั้งหมดนี้จะได้รับฮอร์โมนทดแทน ที่ประกอบด้วย estradiol valerate/levonorgestrel เป็นเวลา 6 เดือน ซึ่งการประเมินอาการของ วัยหมดประจำเดือนของสตรีที่ทำการศึกษานี้ใช้ค่าของ Menopause Rating Scale II (MRS II) ทั้งก่อนและหลังการรักษา จากการศึกษาพบว่าการเปลี่ยนแปลงของค่า MRS II ของสตรีที่ได้การรักษา มีความผิดปกติโดยรวมลดลง ร้อยละ 34.9 ภายหลังจากได้รับการรักษา 3 เดือน และมีค่าลดลงเท่าเดิมจนถึง 6 เดือนของการรักษา เมื่อพิจารณาถึงความเปลี่ยนแปลงของความผิดปกติในแต่ละด้าน พบว่าความผิดปกติทางด้าน somato-vegetative มีค่าลดลงร้อยละ 32.5 และ 35 ภายหลัง 3 เดือนและ 6 เดือนของการรักษาตามลำดับ ความผิดปกติทางด้านอารมณ์และสภาพจิตใจ มีค่าลดลงร้อยละ 34.1 และ 32.9 ภายหลังการรักษา 3 เดือน และ 6 เดือนของการรักษา ตามลำดับ ขณะที่ความผิดปกติ ทางด้านการถ่ายปัสสาวะและระบบอวัยวะสืบพันธุ์มีค่าลดลง ร้อยละ 29.3 ตั้งแต่ 3 เดือนจนถึง 6 เดือนของการรักษา จากการศึกษาครั้งนี้ จึงสรุปได้ว่า การให้ฮอร์โมน ทดแทนที่ประกอบด้วย estradiol valerate/levonorgestrel เป็นเวลา 6 เดือน แก่สตรีวัยใกล้หมดประจำเดือน และสตรีวัยหมดประจำเดือนที่มีอาการของวัยหมดประจำเดือน สามารถลดอาการผิดปกติของวัยหมดประจำเดือนได้ เมื่อประเมินด้วยค่า Menopause Rating Scale II

คำสำคัญ : อาการของวัยหมดประจำเดือน, วัยหมดประจำเดือน, ฮอร์โมนทดแทน, เอสตราไดออล วาเลอเรต/เลโวนอร์เจสเตรล

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