The Metabolic and Bone Density Effects of Continuous Combined 17-beta Estradiol and Noresthisterone Acetate Treatments in Thai Postmenopausal Women : A Double-Blind Placebo-Controlled Trial

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Abstract

Objective: To compare the changes of lipid parameters, liver function tests, fasting plasma glucose and bone density in Thai postmenopausal women who received this combined hormonal treatment and placebo.

Study design: Double-blinded, randomized controlled trial study.

Material and Method: Sixty postmenopausal women attending the menopause clinic at Chulalongkorn Hospital from July, 1996 to December, 1996, were enrolled in the study. The patients were randomized to receive the placebo or drug (17 beta-estradiol 2 mg and norethisterone acetate 1mg) continuously. Patient characteristics, physical examination, liver function tests, fasting plasma glucose, lipid parameters (fasting total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL) and triglyceride level) and bone densitometry were performed before beginning the study. The lipid parameters were repeated at 3, 6 and 12 months. Fasting plasma glucose, liver function tests and bone densitometry were repeated at 12 months.

Results: In the drug group, there were significant changes in the cholesterol at 3, 6 and 12 months when compared to the baseline. There were significant differences at 3, 6 and 12 months when compared between groups. The HDL values were not significantly different within groups. The LDL values at 3, 6, 12 months were significantly lower than the baseline in the drug group when compared within groups and at 6, 12 months in the placebo group. The triglyceride values were not significantly different between groups and within groups. There was no significant change between groups and within groups of fasting plasma glucose, total bilirubin, direct bilirubin, AST, ALT, albumin and globulin. The alkaline phosphatase values were significantly decreased at 12 months in the drug group. The bone density of total BMD and T-score at the spine of the drug group increased significantly at 12 months. The per cent change per year was +5.1. In contrast, the values in the placebo group decreased significantly, the per cent change per year was -0.9. The same pattern was also found in the bone density of the total hip. But when focused to the femoral neck, we found no significant change in both groups.

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Conclusion: This continuous combined treatment resulted in beneficial changes of bone density and lipid profiles. The therapy prevented bone loss and the changes in serum lipoprotein were concordant with a lipid profile associated with a decreased risk of coronary heart disease in Thai postmenopausal women.

Key word : Lipid, Liver Function, Estradiol, Noresthisterone, Menopause

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Estrogen replacement therapy has now been well documented for protection from osteoporosis, prevention of vasomotor symptoms and it reduces the risk of cardiovascular disease in postmenopausal women[1]. The continuous combined treatment with 17 beta estradiol and noresthisterone acetate were more beneficial in producing an atrophic endometrium and amenorrhoea[2,3]. Among many progestrogens, noresthisterone acetate was the most effective in preventing bone loss and inducing amenorrhoea in long term treatments[4-6]. The norethisterone acetate was a 19- norprogestogens known to reduce the HDL- cholesterol fraction when given orally[7]. But when combined with 17-beta estradiol, the marked reduction in low density lipoprotein and cholesterol concentrates still suggests a reduced cardiovascular risk[8].

Up to now there has been no report about the effects of this combined treatment in lipid parameters, liver functions tests and bone density in Thai postmenopausal women. So this study was conducted to compare those changes in Thai postmenopausal women who received this combined hormonal treatment.

MATERIAL AND METHOD

A total of 60 women attending the menopause clinic at Chulalongkorn Hospital from July, 1996 to December, 1996, were enrolled in the study. The study was approved by the ethics committee of Chulalongkorn University Hospital. The women's ages were between 45 and 65 years with intact uterus and diagnosis of menopause by : amenorrhoea for 12 months, Follicle Stimulating Hormones (FSH) >35 IU/L, Estradiol (E_2) <50 pmol/L. The exclusion criteria were; history of estrogen dependent tumor, active or chronic liver disease or history of liver disease where the liver function tests had failed to return to normal, deep vein thrombosis, thromboembolic disorders, cerebrovascular accidents or past history of these conditions associated with estrogen use, abnormal genital bleeding of unknown etiology, porphyria, having had hormone replacement therapy within the past year, uncontrolled hypertension or diabetes mellitus.

All patients were assigned randomly to either the placebo or drug group. During the first three months, 4 cases in the drug group and 3 cases in the placebo group were withdrawn from the study for non-medical reasons. The study group received continuously 2 mg of 17 beta -estradiol and 1 mg of norethisterone acetate daily.

Patient characteristics, physical examination, liver function tests, fasting plasma glucose, lipid parameters (fasting total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL) and triglyceride level) and bone densitometry were performed before beginning the study. The lipid parameters and liver function tests were measured by enzymatic colorismetric methods. Bone mass measurements at hip and spine were performed with a dual energy X-ray absorptiometer (DEXA), Hologic QDR 2000. The lipid parameters were repeated at 3, 6, 12 months. Fasting plasma glucose, liver function tests and bone densitometry were repeated at 12 months.

Statistical analysis of patient characteristics was carried out between groups by using the unpaired student T-test, within the same group by

Table 1. Patient characteristics.

Characteristics	Drug (N=27)		Placebo (N= 26)	
	Mean±SD	Range	Mean±SD	Range
Age (years)	53.4±5.2	46-62	53.7± 4.6	45-64
Duration of menopause (years)	4.8 ± 3.8	1-17	4.9±4.0	1-15
Menarche (years)	13.7± 1.7	11-18	14.1 ± 1.5	12-18
Age at menopause (years)	48.6 ± 3.7	42-56	48.8 ± 3.4	42-54
Weight (kg)	55.2 ± 7.2	40-68	57.5± 9.4	44-83
Height (cm)	152.0 ±4.8	141.5-161	152.6 ± 4.0	144 –161
Systolic blood pressure (mmHg)	118.9 ± 9.8	100-140	117.3 ± 14.6	90-140
Diastolic blood pressure(mmHg)	75.3 ± 7.3	60-90	76.5 ± 9.4	60-88
Parity	2.4± 1.5	0-6	2.6-1.4	0-5

Table 2. Lipid parameters (mean ± SE).

Lipid parameter	Group	At 0 month	At 3 months	At 6 months	At 12 months
Cholesterol (mg/dl)	Drug (N=27)	226.3±5.7	195.8±6.5 *,**	176.7±7.7 *,**	188.3±6.0 *,**
	Placebo (N=26)	242.8±4.1	234.6±7.4 **	204.6±11.4 *,**	218.4±8.8 *,**
HDL (mg/dl)	Drug (N=27)	50.9±3.1	42.7±2.5 **	46.6±2.5	48.2±2.6
	Placebo (N=26)	52.5±2.9	53.3±3.2 **	53.6±3.3	53.7±3.5
LDL (mg/dl)	Drug (N=27)	155.5±6.7	130.0±7.5 *,**	109.7±8.2 *	119.1±6.7 *,**
	Placebo (N=26)	172.9±4.2	164.3±7.8 **	130.7±10.8 *	147.1±9.4 *,**
Triglyceride (mg/dl)	Drug (N=27)	115.6±13.2	109.3±10.3	101.8±10.8	105.1±9.8
	Placebo (N=26)	86.5±6.2	81.6±6.1	101.0±11.6	87.8±7.7

* Significant statistical difference at $p< 0.05$ when comparing within the same group by using ANOVA and compared to the 0 month period within groups, using paired t- test.

** Significant statistical difference at $p< 0.05$ when comparing between groups, using unpaired

using one way-analysis of variance (ANOVA) and compared to the baseline by the paired t-test. The statistical program, SPSS® version 7.5 for Microsoft window® 98, was used for statistical analysis.

RESULTS

There was no statistically significant difference between the groups in any patient characteristics (Table 1). The mean values of plasma lipid and lipoproteins are presented in Table 2. There was no significant difference between the drug group and placebo group at the baseline. The cholesterol values were significantly different at 3, 6 and 12 months when compared between the groups. The drug group had the lower values with statistical significance at 3, 6, 12 months. When compared to the baseline, in the drug group, the mean value was significantly lower at 3, 6, 12 months. In the placebo group, the mean values were significantly lower at 6, 12 months. The HDL values were not significantly different within groups (by ANOVA). But when compared between groups, the mean value at 3 months in the drug group was significantly lower than in the placebo group. The LDL values, when compared within groups, at 3, 6, 12 months were significantly lower than the baseline in the drug group and the values at 6, 12 months were significantly lower than the baseline in the placebo group. There was no difference between groups. The triglyceride values were not significantly different between groups and within groups.

There was no significant change between groups and within groups at 0, 12 months in the values of fasting plasma glucose, total bilirubin, direct bilirubin, AST, ALT, albumin and globulin. Only the alkaline phosphatase values had signifi-

Table 3. Fasting plasma glucose and liver function test parameters (mean ± S.D.).

Parameters	Group	At 0 month	At 12 months
Fasting plasma glucose (mg/dl)	Drug (N=27)	92.4±7.4	86.8±5.4
	Placebo (N=26)	94.6±11.1	93.8±10.7
Total bilirubin (mg/dl)	Drug (N=27)	0.6±0.1	0.6±0.3
	Placebo (N=26)	0.6±0.2	0.6±0.2
Direct bilirubin (mg/dl)	Drug (N=27)	0.1±0.2	0.1±0.01
	Placebo (N=26)	0.1±0.1	0.1±0.1
AST (unit / L)	Drug (N=27)	24.1±8.22	19.5±5.4
	Placebo (N=26)	21.4±4.7	22.2±7.3
ALT (unit / L)	Drug (N=27)	22.4±11.6	13.0±5.2
	Placebo (N=26)	19.2±9.4	18.4±14.5
Albumin (G/dl)	Drug (N=27)	4.6±0.9	4.6±0.8
	Placebo (N=26)	4.7±0.9	4.9±0.3
Globulin (G/dl)	Drug (N=27)	3.0±0.6	2.9±0.7
	Placebo (N=26)	2.8±0.5	2.8±0.6
Alkaline phosphatase (unit / L)	Drug (N=27)	189.8±53.1	125.7±32.3*,**
	Placebo (N=26)	196.4±55.3	189.9±45.1**

* Significant statistical difference at $p<0.05$ when comparing to the 0 month period within the same groups, using paired t- test.

** Significant statistical difference at $p<0.05$ when comparing between groups, using unpaired t-test.

cantly decreased at 12 months referring to the baseline in the drug group. This value was significantly lower than with the placebo at the same period (Table 3).

In the drug group, the bone density values of total BMD and T-score at the spine increased significantly at 12 months referring to the baseline. The mean±SD of the per cent change per year was +5.1±4.1. In contrast, the values in the placebo group decreased significantly at 12 months and the mean±SD of the per cent change per year was –0.9±3.1. The same pattern was also found in the bone density of total hip. But when focusing only on the femoral neck, we found no significant change in both groups. At the ward, the total BMD and T-score increased significantly in the drug group. No similar change was found in the placebo group. At 12 months the values of the drug group were significantly higher than the placebo group.

DISCUSSION

The most beneficial metabolic effect of hormone replacement therapy is the reduction in the total cholesterol concentration. It is due to up-regulation of LDL receptor activity in the liver and peripheral tissues[9,10] resulting in increased LDL uptake from the circulation. In our study, this effect was evident after 3 months. The patients in the placebo group had also decreased LDL levels which may be due to the diet control based on the health education in the menopause clinic but the hormonal treatments were more effective. This reduction effect was also noted in the total cholesterol. These results were consistent with the findings in Euro-

Table 4. Bone densitometry (mean ± S.D.).

Bone densitometry	Drug (Mean±S.D.) N= 27		Placebo (Mean±S.D.) N= 26	
	0 month	12 months	0 month	12 months
Spine				
• Total BMD	0.8±0.1	0.9±0.1 *,**	0.9±0.1	0.8±0.1 *,**
• T-score	-1.9±0.9	-1.5±0.9 *,**	-1.7±1.1	-1.8±1.1 *,**
• % change / year	-	+5.1±4.1	-	-0.9±3.1
Total hip				
• Total BMD	0.7±0.1	0.8±0.1 *,**	0.8±0.1	0.7±0.1 *,**
• T-score	-1.4±0.9	-1.3±0.9 *,**	-1.3±0.9	-1.4±0.9 *,**
• % change / year	-	+2.6±2.4	-	-1.2±2.2
Femoral neck				
• Total BMD	0.7±0.1	0.7±0.1	0.7±0.1	0.7±0.1
• T-score	-2.6±0.9	-2.0±0.8	-1.7±1.1	-1.8±1.1
• % change / year	-	+0.6±2.4	-	-0.9±2.9
Ward's area				
• Total BMD	0.5±0.1	0.6±0.1 *,**	0.6±0.1	0.5±0.1 **
• T-score	-2.2±1.3	-2.0±1.2 *,**	-2.2±1.3	-2.4±1.2 **
• % change / year	-	+4.5±3.6	-	-2.5±5.5

* Significant statistical difference at $p< 0.05$ when comparing to the 0 month period within the same groups, using paired t- test.

** Significant statistical difference at $p< 0.05$ when comparing between groups, using unpaired t-test.

pean studies[8,11]. Estrogen alone increased triglycerides by induction of hepatic over- production of triglyceride- rich lipoprotein[12,13]. But when combined with progestrogen, the triglyceride level was elevated. This is due to the ability of the progestin to increase the catabolism of triglyceride- rich lipoprotein[14]. In our study, the progestogenic effect on triglycerides in Thai women was not as prominent as in other reports[11,15-19]. We found the triglyceride levels were unchanged.

Estrogen is commonly perceived as an agent that raises HDL concentrations,[20,21] whereas, progestin increases the catabolism of HDL[22,23]. But the changes seen with the current low dose regimen are subtle[24,25]. The progestin in the continuous combined treatment may overcome the estrogen and induce decreases in HDL protein synthesis[26]. There have been reports of decreased HDL levels due to this continuous combined treatment in European women[15,27]. We found only a slight decrease of HDL in the drug group at 3 months. This different response for HDL and triglycerides may be explained by racial and dietary differences. Even this combined treatment eliminated the increase in HDL which could be observed with estrogen monotherapy, the decrease in total cholesterol and LDL without any change in HDL and triglycerides in Thai postmenopausal women seemed to be beneficial in that it decreased the risk of coronary heart disease[29-31].

We found no changes in liver function tests and fasting plasma glucose. The alkaline phosphatase decreased significantly in the drug group due to the anti-osteoclastic activity of estrogen therapy[32]. It has been well established that estrogen deficiency is the dominant pathogenic factor for osteoporosis in postmenopausal women. The decline in estrogen levels causes an imbalance between bone resorption and bone formation resulting in accelerated bone loss. Concomitant progestogen therapy may enhance the bone-conserving effects of estrogen[12]. There have been reports of significant increases in bone mineral contents and bone mass during sequential or continuous combined therapy consisting of 17 beta-estradiol and noresthisterone acetate[17,33,34]. Noresthisterone acetate may prevent bone loss by uncoupling bone formation and resorption[35]. Our study indicated that this continuous combined treatment was more effective in prevention of bone loss and can increase the bone density when compared to the placebo. These effects were more prominent in the spine than the total hip but were not found in the femoral neck which could be explained by the more significant estrogenic effects on trabecular bones than on cortical bones[32]. Mostly the age (or the aging process) was the factor important for the low bone density of the cortical bone[32]. These changes were consistent with other studies[17,33,36-40].

According to our data, this continuous combined treatment resulted in beneficial changes of bone density and lipid profiles. The therapy prevented bone loss and the changes in serum lipoprotein were concordant with a lipid profile associated with a decreased risk of coronary heart disease in Thai postmenopausal women.

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การศึกษาเปรียบเทียบเมตาบอลิคและความหนาแน่นของกระดูกในสตรีไทยหมดประจำเดือนที่รักษาโดยควบยา 17–บีตาเอสตราดิออลและนอร์เอสธิสเตอโรนระยะยาว : การศึกษาแบบดับเบิลบลายด์ พลาซิโบ–คอนโทรล

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วัตถุประสงค์ : เพื่อศึกษาเปรียบเทียบการเปลี่ยนแปลงของไขมัน หน้าที่การทำงานของตับ ปริมาณน้ำตาลในเลือดหลังอดอาหาร และความหนาแน่นของกระดูกในสตรีไทยวัยหลังหมดประจำเดือนที่ได้รับยา 17 beta–estradiol and norethisterone acetate เทียบกับยาหลอก.

รูปแบบการศึกษา : Double blind, randomized controlled trial

วัสดุและวิธีการ : ทำการสุ่มแบ่งกลุ่มสตรีไทยวัยหลังหมดประจำเดือนจำนวน 60 คนที่มารับบริการที่คลินิกวัยหมดระดู ระหว่างเดือนกรกฎาคม ถึงเดือนธันวาคม 2539 เป็นสองกลุ่ม โดยผู้รับบริการจะได้รับยาหลอก หรือ 17 beta–estradiol 2 มก. และ norethisterone acetate 1 มก. อย่างต่อเนื่อง ทำการบันทึกข้อมูลทั่วไป การตรวจร่างกายทั่วไปและการตรวจทางนรีเวช ตรวจหน้าที่การทำงานของตับ ปริมาณน้ำตาลในเลือดหลังอดอาหาร ค่าไขมันชนิดต่าง ๆ (Fasting total cholesterol, low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL) and triglyceride level) และความหนาแน่นของกระดูก ก่อนเริ่มการศึกษา จากนั้นทำการตรวจค่าไขมันชนิดต่าง ๆ ซ้ำที่เวลา 3, 6, 12 เดือน ตรวจหน้าที่การทำงานของตับ ปริมาณน้ำตาลในเลือดหลังอดอาหาร ซ้ำที่เวลา 12 เดือน

ผลการศึกษา : ในกลุ่มที่ใช้ยาจริงพบการเปลี่ยนแปลงของ Cholesterol อย่างมีนัยสำคัญทางสถิติที่เวลา 3, 6 และ 12 เดือน เมื่อเทียบกับก่อนเริ่มการศึกษาในกลุ่มเดียวกัน และพบการเปลี่ยนแปลงอย่างมีนัยสำคัญที่เวลา 3, 6 และ 12 เดือนเมื่อเทียบระหว่างกลุ่ม พบการแตกต่างอย่างมีนัยสำคัญในกลุ่มเดียวกันของ HDL ค่า LDL ลดลงอย่างมีนัยสำคัญเมื่อเทียบกับก่อนการศึกษาที่เวลา 3, 6, 12 เดือนในกลุ่มที่ใช้ยาจริงและที่เวลา 6, 12 เดือนในกลุ่มที่ใช้ยาหลอก ไม่พบการแตกต่างอย่างมีนัยสำคัญระหว่างกลุ่มและในกลุ่มเดียวกันของค่าไขมัน Triglyceride ไม่พบการแตกต่างอย่างมีนัยสำคัญระหว่างกลุ่มและในกลุ่มเดียวกันของปริมาณน้ำตาลในเลือดหลังอดอาหาร, Total bilirubin Direct bilirubin AST, ALT, albumin และ globulin พบว่าค่า Alkaline phosphatase ลดลงอย่างมีนัยสำคัญทางสถิติที่เวลา 12 เดือนในกลุ่มที่ใช้ยาจริง ความหนาแน่นของกระดูก (Total BMD and T–score) ที่กระดูกสันหลังเพิ่มขึ้นอย่างมีนัยสำคัญที่เวลา 12 เดือน ค่าเฉลี่ยของเปอร์เซ็นต์ของการเปลี่ยนแปลงต่อปีคือ +5.1 ในทางตรงกันข้ามกลุ่มที่ใช้ยาหลอกมีค่าลดลงอย่างมีนัยสำคัญ ค่าเฉลี่ยของเปอร์เซ็นต์ของการเปลี่ยนแปลงต่อปีคือ –0.9 พบการเปลี่ยนแปลงแบบเดียวกันในความหนาแน่นของกระดูกสะโพกโดยรวม แต่เมื่อพิจารณาเฉพาะที่คอของกระดูก Femoral ไม่พบการเปลี่ยนแปลงอย่างมีนัยสำคัญในทั้งสองกลุ่ม

สรุปผลการศึกษา : การใช้ฮอร์โมนรวมชนิดต่อเนื่องนี้ทำให้เกิดการเปลี่ยนแปลงที่มีประโยชน์ต่อความหนาแน่นของกระดูกและไขมัน ป้องกันการสูญเสียเนื้อกระดูกและการเปลี่ยนแปลงของ Lipoprotein เข้าได้กับลักษณะของไขมันที่จะลดความเสี่ยงต่อการเกิดโรคหัวใจในสตรีไทยวัยหลังหมดประจำเดือน

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