Comparative Effects of 17-ß Estradiol Gel and Conjugated Estrogen on Climacteric Symptoms and Hormonal Levels in Oophorectomized Women

Rudi Sirimongkolkasem MD*,
Aram Rojanasakul MD*,
Nattapong Israngura Na Ayudhya MD*,
Varavudh Sumawong MD*,
La-or Chailukit†.

*Department of Obstetrics and Gynaecology,
†Department of Medicine,
Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand

Abstract: *The aim of this study is to compare the effects of estradiol gel and conjugated estrogen as treatment for climacteric symptoms and their effects on hormonal levels in oophorectomized women. The patients had hysterectomy and bilateral oophorectomy performed at least 6 weeks prior to estrogen treatment. They were randomly allocated into two groups. Group 1 (21 patients) received 17-ß estradiol gel 2.5 gm percutaneously once daily. Group 2 (21 patients) received 0.625 mg of conjugated estrogen orally. These were given for 3 weeks. Both groups had similar mean age, weight and height. After treatment the climacteric symptoms decreased in all patients. The patients reported that treatments were favourable. No significant adverse effect of the drugs was observed. Mean serum estradiol level in both groups increased to early follicular phase level. (from 11.05±8.01 and 10.11±4.48 to 67.83±64.32 and 59.89±42.96 pg/ml in group 1 and 2, respectively). In conclusion conjugated estrogen and 17-ß estradiol at dosage used in this study were comparable in clinical and hormonal effects. (Thai J Obstet Gynaecol 1989; 1:.25-30)*

Key words: 17-ß estradiol gel, conjugated estrogen, climacteric symptoms, oophorectomized women

The benefit of estrogen replacement therapy in postmenopausal women is obvious. It relieves climacteric symptoms and also abolishes or minimizes postmenopausal bone loss.[1-5] Oral substitution with conjugated estrogen is at present the most common therapy. But it is, however, claimed to be unphysiologic due to a higher level of estrone to estradiol ratio and high concentration of hormone in portal circulation, which will be further converted in the liver.[6] Recently percutaneous administration of 17 -ß estradiol in a gel form was introduced in Thailand, offering an alternative route to that of oral estrogen. Compared with

the oral treatment, percutaneous administration of estradiol may have theoretical advantage with respect to liver metabolism because the hormone will directly enter peripheral circulation without passing through enterohepatic circulation. There is, however, potential disadvantage related to the specific kinetics of this route.[7]

The aim of this study is to compare the effects of percutaneous 17-ß estradiol gel and conjugated estrogen given orally as treatment for climacteric symptoms and their effects on hormonal levels in oophorectomized women.

Materials and Methods

This prospective study was conducted at Ramathibodi Hospital during May 1987 to September 1987. Forty-two healthy women aged between 25 to 53 years, who had hysterectomy and bilateral oophorectomy carried out for benign causes, were recruited in this study. Their operations were performed at least 6 weeks previously. They had at least one climacteric symptom. All women did not receive any hormonal treatment for at least 3 months preceeding the study. None had a history of liver disease, vascular disease, diabetes, hypertension or any contraindication to estrogen therapy. The subjects were randomly allocated to two groups. A hydroalcoholic gel containing 17-ß estradiol (Estrogel®, Besin-lscovesco, France) was prescribed for the first group. The dosage was 2.5 gm of gel (1.5 mg of 17 -ß estradiol) applied once daily in the morning to the skin of the abdomen and left to dry for a few minutes before dressing. The second group received 0.625 mg of conjugated estrogen (Premarin®, Ayerst) in a single dose orally in the morning. Before starting treatment, all subjects were asked about the climacteric symptoms, and blood samples were taken for the assays of follicular stimulating hormone (FSH), luteinizing hormone (LH) and estradiol levels. All patients were instructed to record any complication in the treatment. After 3 weeks of treatment all subjects were evaluated for the improvement in symptoms and complication of treatment. Blood samples were again taken for the hormonal assays.

Serum LH, FSH and estradiol were determined by radioimmunoassay using commericial kits (Diagnostic Product Co, Los Angeles, CA). Student *t*- test was used to compare the mean value of clinical effects and hormonal levels between the two groups.

Results

There were 21 patients in each group. During the treatment 3 women in the "17-ß estradiol" group were lost to follow up for unknown reasons. Two subjects in the "Conjugated estrogen" group were excluded from the study due to the drug being taken irregularly.

There were no significant differences in mean age, weight and height for both groups (Table 1). Before starting the treatment, all subjects had serum estradiol level in the postmenopausal range with elevated level of FSH and LH (Table 2). The mean level of LH was higher in

Table 1 Pretreàtment clinical parameters

Parameters	17-ß estradiol n = 18 Mean ± SD	Conjugated estrogen n = 19 Mean ± SD
Age (yr)	43.11 ± 5.42	42.7 ± 3.79
Weight (kg)	52.43 ± 8.11	55.95 ± 6.90
Height (cm)	154.13 ± 4.29	152.32 ± 6.40

Table 2 Pretreatment hormonal levels

Hormones	17-ß estradiol n = 18 Mean ± SD	Conjugated estrogen n = 19 Mean ± SD
LH (mIU/ml)	123.61 ± 49.20	86.47 ± 43.39*
FSH (mIU/ml)	92.56 ± 24.01	83.79 ± 27.10
Estradiol (pg/ml)	11.50 ± 8.01	10.11 ± 4.48

* significant difference, $p < 0.05$

Table 3 Clinical responses of the treatment

Symptoms	17-ß estradiol		Conjugated estrogen	
	n	%	n	%
Hot flush	15/15	100	18/18	100
Sweating	13/13	100	18/18	100
Insomnia	9/11	82	11/11	100
Headache	6/8	75	6/7	86

n = number of patients with improvement of symptoms/ number of patients with symptoms before treatment.

the "17-ß estradiol" group. However, all subjects had LH level in the postmenopausal range.

After 3 weeks of treatment, the climacteric symptoms i.e. hot flushes and sweating subjectively decreased in all patients in both groups. Other nervous symptoms such as insomnia and headache had also lessened (Table 3). The patients did not complain about the treatment and judged the treatment as favourable in both groups. No significant adverse effect of the drugs was reported in either group.

Hormonal levels after 3 weeks of treatment changed significantly. Mean serum estradiol in "17-ß estradiol" group and "Conjugated estrogen" group increased from 11.05±8.01 and 10.11±4.48 to 67.83±64.32 and 59.89±42.96 pg/ml, respectively (Fig. 1). Mean serum FSH decreased in both groups (Fig 2). For serum LH, the level did not change significantly after treatment in both groups and remained in the postmenopausal range.

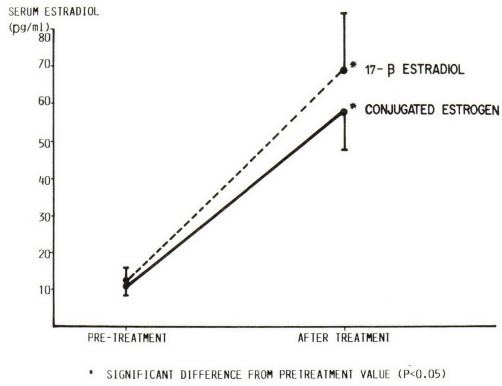

Fig 1. Serum estradiol before and after treatment

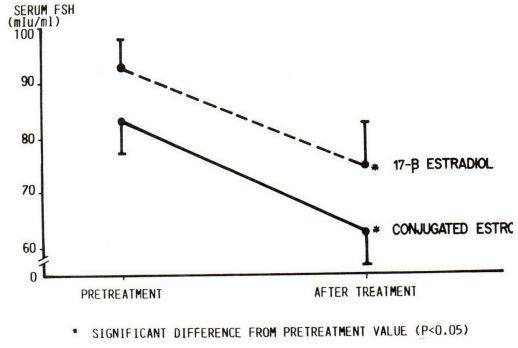

Fig 2. Serum FSH before and after treatment

Discussion

In this study, the effects of subcutaneous 2.5 gm of 17-ß estradiol gel and orally 0.625 mg of conjugated estrogen on climacteric symptoms and hormonal levels were compared. All subjects in both groups had decreased hot flushes and sweating, symptoms claimed to be due to estrogen deprivation.[8] Other symptoms which might be indirect effects from estrogen deficiency such as insomnia and headache were also improved.

The present study also showed that percutaneous administration of drug results in a significant absorption of estrogen. The peripheral estradiol levels after percutaneous dose of 2.5 gm of 17-ß estradiol were the same magnitude as after oral administration of 0.625 mg of conjugated estrogen and corresponded to the levels at early proliferative phase of menstrual cycle. The lowest daily dose of conjugated estrogen that consistently protects against bone loss was reported to be 0.625 mg.[9-11] So percutaneous 17 -ß estradiol at this dosage may be an effective preventive therapy of postmenopausal bone loss. The therapeutic effectiveness of estradiol level for relieving vasomotor symptoms was 40-50 pg/ml.[12] Thus, application of 2.5 gm of 17 -ß estradiol gel daily should be enough. In this study, however, there was a wide range of estradiol level after treatment which emphasized the necessity to individualize the dosage.[12] Several factors such as the application site, time of day, humidity and climate might effect the absorption of hormone through the skin. Previous studies about the use of percutaneous estradiol were conducted on Caucasians. The results may not be applicable to population in different regions. This study in Asian women, however, showed that the percutaneous administration of estrogen could fairly increase estradiol level.

After 3 weeks of treatment, both groups had significantly decreased level of FSH, but remained in postmenopausal range. This finding agreed with other studies that negative feed back of postmenopausal women is still preserved. [13,14] But it could not lower the level of the hormone to premenopausal level which could be due to insufficient level of estradiol.

In this study there was no reported side effects from treatment. There were no allergic reactions at the site of dermal application. All patients using subcutaneous 17-ß estradiol gel judged that the treatments were favourable.

Since the effectiveness of estrogen replacement therapy is obvious no matter what kind of estrogen is used, natural or synthetic estrogen, either in oral or in parenteral forms, might be considered as effective as long as they are given in sufficent doses. Percutaneous application provides an alternative to the oral route. Zondex[6] was the first to demonstrate that estrogens were absorbed through the skin of ovariectomized mice in quantities sufficient to produce estrus. The difference between the phamacodynamic of oral and percutaneous treatment is that following oral treatment, the intestinal absorption is rapid and yields extremely high concentration of hormone in portal

circulation. For topical administration of 17-ß estradiol, the hormone enters the peripheral circulation without passing the entero-hepatic circulation. The bypass of liver circulation may be beneficial since some side effects and risks associated with estrogen replacement therapy are known to stem from the hormone's impact on the liver.[5,6,13,15] Previous studies have shown that topical administration of 17-ß estradiol does not change the concentration of hepatic protein and does not so through the liver first. The conversion of estradiol to estrone, which is a consequence of the oral administration, is less pronounced so that estrone to estradiol ratio in the circulation will more closely resemble the physiological state of fertile women.[6,15,16] Estrone level was not assayed in this study due to technical problems. In comparison with the oral route, the increase in peripheral estrogen of percutaneous treatment was quite slow, less pronounced and had a longer maintenance of this level.[17]

In conclusion, both orally 0.625 mg of conjugated estrogen and 1.5 mg of 17-ß estradiol percutaneously were compared for clinical and hormonal effects. Further studies are needed to clarify the clinical significance of the theoretical advantages of topical estradiol application.

References

1. Brincat M, Moniz CF, Kabalan S, et al. Decline in skin collagen content and metacarpal index after the menopause and its prevention with sex hormone replacement. Br J Obstet Gynaecol 1987;94:126-9.
2. Nilas L, Christiansen C. Bone mass and its relationship to age and the menopause. J Clin Endocrinol Metab 1987;65:697-702.
3. Quigley TME, Martin PL, Burnier AM, Brooks P. Estrogen therapy arrests bone loss in elderly women. Am J Obstet Gynecol 1987;156:1516-23.
4. Riis BJ, Thomsen K, Strom V, Christiansen C. The effects of percutaneous estradiol and natural progesterone on postmenopausal bone loss. Am J Obstet Gynecol 1987;156:61-7.
5. Riggs BL. Pathogenesis of osteoporosis. Am J Obstet Gynecol 1987;156:1342-6.
6. Holst J. Percutaneous estrogen therapy. Acta Obstet Gynecol Scand 1983;115:7s-30s.
7. Nilsson B, Holst J, Schoultz V. Serum levels of unbound 17-ß oestradiol during oral and percutaneous postmenopausal replacement therapy. Br J Obstet Gynaecol 1984; 91:1031-6.
8. Rebar RW, Spitzer IB. The physiology and measurement of hot flushes. Am J Obstet Gynecol 1987;156:1284-8.
9. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. Obstet Gynecol 1984;63:759-63.
10. Geola FL, Fruman AM, Tataryn I, et al. Biological effects of various doses of conjugated equine estrogen in postmenopausal women. J Clin Endocrinol Metab 1980; 51:620-5.
11. Dymling JF. Osteoporosis - Possible benefits of treatment with gonadal steroids. Acta Obstet Gynecol 1987;40:66s-9s.
12. Nichols KC, Schenkel L, Benson H. 17-ß estradiol for postmenopausal estrogen replacement therapy. Obstet Gynecol Surv 1984;39:230-45.
13. Nishi T, Yagi S, Nakano K. Feedback of estrogen in postmenopausal women. Acta Obstet Gynecol Scand 1987;66:915-9.
14. Scott JC, Cumming DC. The menopause. Currents Problems Obstet Gynecol Fertil 1985;8:8-10.
15. Judd H. Efficacy of transdermal estradiol. Am J Obstet Gynecol 1987;156:1326-31.
16. Lignieres BD, Basdevant A, Thomas G, et al. Biological effects of estradiol 17-ß in

postmenopausal women : Oral versus percutaneous administration. J Clin Endocrinol Metab 1986;62:536-41.

17. Lyrenas S, Carlstrom K, Backstrom T, Schoultz BV. A comparison of serum estrogen level after percutaneous and oral administration of oestradiol-17 ß. Br J Obstet Gynaecol 1981;88:181-7.