Menopause: The Journal of The North American Menopause Society
Vol. 8, No. 5, pp. 353–360

Pharmacokinetics and pharmacodynamics of 25-mg estradiol implants in postmenopausal Mexican women

Ma. del Carmen Cravioto, MD,[1] Fernando Larrea, MD,[1] Ninoska E. Delgado, MD,[1] Alicia Rico Escobar, MD,[1] Vicente Díaz-Sánchez, MD,[1] Jorge Domínguez, MD,[2] and Rebeca Ponce de León, MD[3]

ABSTRACT

Objective: To assess the serum concentrations of estradiol (E_2), estrone (E_1), gonadotrophins, sex hormone-binding globulin, and lipids, and to determine degree of symptom relief after subcutaneous implantation of 25 mg estradiol in postmenopausal Mexican women.

Design: Fifteen postmenopausal, hysterectomized women participated in an open, observational study. Blood samples were obtained before implantation and at regular intervals during a study period of 24 weeks. Climacteric symptoms were evaluated by means of the Greene climacteric scale. Wilcoxon's test was performed on the paired results of pre- and postimplantation values.

Results: Serum concentrations of E_2 obtained after implantation were fairly constant, remaining within the early follicular range for the entire study period of 24 weeks, and were associated with significant symptom relief. A physiological, premenopausal E_2:E_1 ratio was achieved. No significant metabolic changes occurred. Side effects were estrogenic in nature and no removal of implant was required.

Conclusions: Subcutaneous implantation of 25 mg estradiol results in physiological, premenopausal estrogen concentrations in most women and is associated with considerable symptom relief without inducing significant adverse metabolic effects.

Key Words: Estradiol – Implants – Estrogen replacement therapy – Pharmacodynamics – Subcutaneous implants – Long-term ERT.

With increasing life expectancy, a growing number of Mexican women reach the age of menopause, and the mean period that women live in postmenopause has been increased to almost 30 years. The disturbed balance between estrogen and gonadotrophin production during the perimenopause may result in varying degrees of discomfort, such as vasomotor symptoms (hot flushes and night sweats), depressive mood symptoms, and sleeping disorders. In addition, long-term estrogen deficiency in the postmenopause is associated with urogenital atrophy, increased risk of osteoporosis, and increased cardiovascular risk. Both estrogen replacement therapy (ERT) and hormone replacement therapy (HRT) have proven to be effective for the treatment of climacteric and urogenital problems and for reducing the risk of osteoporosis and possibly cardiovascular disease.[1–3] With a growing number of postmenopausal women, the interest in ERT/HRT has increased, and varying possibilities of ERT/HRT have been investigated.

Oral estrogen therapy is effective but has some disadvantages. After absorption into the blood, a large part of an oral estradiol (E_2) dose is directly converted within the gut wall and liver to estrone (E_1) and pharmacologically inactive metabolites.[4] Consequently, oral estrogen has to be given in relatively large doses to produce physiological premenopausal E_2 levels, and

Received January 29, 2001; revised and accepted April 18, 2001.

From the [1]Department of Reproductive Biology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, [2]Organon Mexicana S.A. de C.V., [3]Estadísticos y Clínicos Asociados S.A. de C.V., Mexico City, México.

Address reprint requests to Ma. del Carmen Cravioto, MD, Department of Reproductive Biology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Vasco de Quiroga No. 15, 14000 Mexico City, Mexico.

detrimental hepatic and metabolic effects may result.[5,6] Because of a substantial oxidation of E_2 to E_1 during oral E_2 treatment, the normal premenopausal E_2:E_1 ratio of 2:1 cannot be achieved.[5,6] The relatively high E_1 levels that are achieved with oral estrogens are indicative of various metabolic changes.[5]

Subcutaneous administered E_2 implants avoid this hepatic first-pass effect. As a result, it has less effect on liver metabolism[7–9] and produces a more physiological premenopausal E_2:E_1 ratio.[9–14] In addition, subcutaneous E_2 implant therapy guarantees optimal adherence to therapy and provides more stable plasma E_2 levels as compared to the oral route of administration.

Several reports have demonstrated the efficacy of the 20- or 25-mg E_2 implants in relieving climacteric symptoms.[7–9,14,15] In addition, studies have reported on the pharmacokinetic data of the 25-mg E_2 implant. As it has been shown with other routes of estrogen administration,[16,17] large interindividual differences in E_2 plasma levels have been described. Differences in metabolism, body weight, fat mass, and endogenous E_2 production may play a role. No studies on the use of 25-mg E_2 implants have been performed in Latin America. This study has been designed to determine the pharmacokinetic and pharmacodynamic profile of E_2 implants in postmenopausal Mexican women. In addition, the effects on climacteric symptoms and safety parameters have been reported.

METHODS

Subjects

All subjects gave written consent after being fully informed about the study protocol and objectives. The study protocol was approved by the Ethics Committee of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán and also by the Ministry of Health.

Hysterectomized, postmenopausal women attending the Reproductive Health Clinic who fulfilled the selection criteria were invited to participate in the study. The inclusion criteria were the following: age <55 years, hysterectomy with or without oophorectomy, serum follicle-stimulating hormone (FSH) > 20 IU/L, with or without climacteric symptoms, without HRT or ERT during the previous 3 months, and without contraindications to estrogens use. The exclusion criteria were the following: history or presence of thromboembolic events, breast cancer, or acute or chronic active liver disease; history of endometrial cancer, jaundice in pregnancy, or jaundice due to the use of steroids; undiagnosed vaginal bleeding, porphyria, known or suspected estrogen-dependent tumor; and history of severe pruritus, herpes gestationis, or otosclerosis during pregnancy.

Design

This was an observational, open, single-dose pharmacodynamics study, with the main objective of assessing the serum levels of E_2, E_1, gonadotrophins, sex hormone-binding globulin (SHBG), and lipids after 25-mg estradiol implant. Due to the nature of these types of studies and their complexity (more rigorously controlled than any other type of clinical trial), pharmacodynamic studies are commonly designed without a control group and with a small sample size.

Baseline evaluation included medical history, physical examination, routine laboratory screening tests, mammography, and, when required, transvaginal ultrasound. Body weight, height, and blood pressure of each subject were registered by one investigator. Later on, each woman received one 25-mg estradiol implant (Riselle, Organon Laboratories, Cambridge, UK). The implant (2.2 mm in diameter) was inserted under the skin of the buttock under local anaesthetic by means of the supplied disposable implanter.

Blood samples for determination of E_2, E_1, FSH, and luteinizing hormone (LH) were obtained before the insertion of the implant and subsequently at regular intervals (after 2, 4, 6, 8, 10, and 12 h). These hormonal levels were also measured at all follow-up visits after 1, 2, and 4 weeks and then every 4 weeks until the completion of the study (after 24 weeks). SHBG levels were determined at baseline and at all follow-up visits.

Climacteric symptoms were evaluated by means of the Greene climacteric scale.[18] This scale distinguishes 21 different symptoms clustered into four subclasses: 11 psychological symptoms (subdivided in 6 anxiety symptoms and 5 depression symptoms), 7 somatic symptoms (e.g., headaches, muscle and joint pains), 2 vasomotor symptoms (hot flushes and night sweating), and 1 sexual symptom (loss of sexual interest). Each symptom score ranges from 0 ("not at all") to 3 ("quite a bit"). The questionnaire of the Greene climacteric scale was completed at baseline and after 8, 16, and 24 weeks. At all follow-up visits, subjects were physically examined, including breast examination and measurement of blood pressure, weight, body mass index (BMI), and hip and waist perimeters. Subjects were asked about the occurrence of adverse events, and the implant site was inspected.

Blood chemistry (glucose, urea, creatinine) and serum lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein choles-

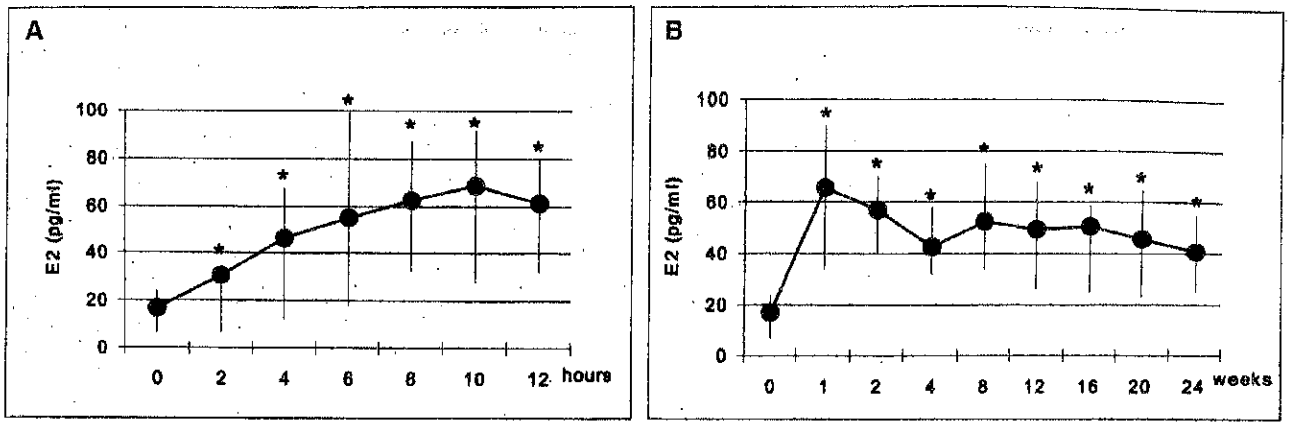

FIG. 1. Mean estradiol (E_2) serum levels after insertion of one 25-mg E_2 implant (Riselle) in postmenopausal women ($n = 15$) at regular intervals on the day of insertion (A) and at follow-up visits during a period of 24 weeks (B). Vertical lines represent the 25 and 75 percentiles. *, statistically significant change compared with baseline ($p < 0.05$).

TABLE 1. *Serum estrogens and gonadotrophins concentrations at different times during 24 weeks after 25-mg E_2 implantation*

		Week								
Variable		Baseline	1	2	4	8	12	16	20	24
Estrone (pg/mL)	Mean ± SD	19 ± 18	43 ± 20[c]	36 ± 21[b]	32 ± 16[c]	33 ± 16[a]	42 ± 22[a]	29 ± 16[a]	31 ± 14[a]	30 ± 15[a]
	Median	13	43	33	27	30	38	31	32	30
	Min-max	7–69	7–77	7–82	7–59	7–61	18–97	7–59	5–52	7–62
Estradiol (pg/mL)	Mean ± SD	17 ± 15	66 ± 37[c]	57 ± 34[c]	43 ± 16[c]	53 ± 24[c]	49 ± 31[b]	50 ± 31[b]	46 ± 32[b]	41 ± 23[b]
	Median	7	61	48	41	53	40	48	31	39
	Min-max	7–51	18–165	21–164	14–64	11–104	19–123	17–122	15–127	14–98
E_2:E_1	Mean ± SD	1.0 ± 0.7	3.0 ± 5.5[a]	2.9 ± 5.3[b]	1.7 ± 1.3[a]	2.4 ± 2.6[b]	1.3 ± 0.8	1.9 ± 1.0[b]	1.82 ± 1.5[b]	1.9 ± 1.9[b]
	Median	0.9	1.5	1.4	1.2	1.4	1.2	1.8	1.3	1.3
	Min-max	0.2–2.8	0.5–22.0	0.5–21.8	0.6–5.5	0.2–10.0	0.3–3.2	0.7–4.6	0.6–5.8	0.5–7.3
LH (IU/L)	Mean ± SD	17 ± 10	16 ± 11	12 ± 6	11 ± 6[a]	10 ± 7[a]	6 ± 5[b]	7 ± 5[b]	8 ± 7[b]	8 ± 7[b]
	Median	18	13	14	9	8	4	6	4	6
	Min-max	0.2–38	4.0–51	0.2–24	2.0–25	0.2–25	2.0–17	0.2–17	0.2–29	0.2–26
FSH (IU/L)	Mean ± SD	48 ± 34	34 ± 27[b]	31 ± 25[b]	27 ± 22[b]	21 ± 19[c]	17 ± 21[b]	21 ± 24[c]	23 ± 26[b]	23 ± 28[c]
	Median	46	28	26	21	17	14	12	11	11
	Min-max	2.0–130	7.0–114	4.0–102	4.0–85	3.0–71	3.0–80	2.0–89	2.0–97	3.0–112

E_2, estradiol; E_1, estrone; LH, luteinizing hormone; FSH, follicle-stimulating hormone.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$.

terol) were determined at baseline and 12 and 24 weeks after implantation. Serum electrolytes (sodium, potassium), liver parameters (albumin, total proteins, aspartate aminotranspherase, alanine aminotranspherase, alkaline phosphatase, direct and indirect bilirubin), and antithrombin III (AT-III) were measured at baseline and repeated after 12 weeks.

Statistical analysis

For all continuous variables, summary statistics were presented, including means, medians, standard deviations, ranges, and 25 and 75 percentiles. Wilcoxon's test was performed on the paired results of pre- and postimplantation values. Wilcoxon's test was used because the data were not normally distributed.

RESULTS

All women completed the study. In addition to being hysterectomized, 11 women were also oophorectomized. Their mean hormone levels at baseline were 48 IU/L FSH (range, 2–130 IU/L) and 17 pg/mL E_2

(range, 7–51 pg/mL). This wide range of hormone levels is explained by the inclusion of one subject, who had a normal FSH value at baseline, although she had a postmenopausal FSH value >20 IU/L in her screening sample. This woman, for whom diagnosis was difficult because she was hysterectomized, probably was perimenopausal because variation in gonadotrophin values is not uncommon in this phase. Mean age was 48.8 years, ranging from 43 to 55 years. Mean BMI was 28.5 kg/m^2. Physical examinations did not reveal any abnormalities. Slight mammographic abnormalities in three subjects and ultrasonically detected ovarian microcysts in one subject were no reason for exclusion. Blood pressure and hematology values were within normal limits.

Estrogens

After insertion of the implant, the mean E_2 level increased immediately from 17 pg/mL before implantation to 31 pg/mL after 2 h, reaching a maximum of 68 pg/mL after 10 h (Fig. 1A). The absorption profiles showed large interindividual variations, reflected by the 3- to 5-fold difference between the 25 and 75 percentiles. At the first follow-up visit (1 week after insertion), the mean E_2 level was still >60 pg/mL (Fig. 1B and Table 1). Thereafter, a gradual decrease was observed, and intersubject variations narrowed. Mean E_2 level remained >40 pg/mL until the end of the study period (after 24 weeks). All mean E_2 values measured from 2 h to 24 weeks after implantation were significantly increased ($p < 0.005$). In one-fourth of the subjects, the serum E_2 level decreased to a level <25 pg/mL (100 pmol/L) within 24 weeks of implantation.

Mean E_1 levels did not show a statistically significant increase during the first 12 h. After 1 week, a significant increase ($p < 0.001$) of the mean E_1 value (from 19 pg/mL to 43 pg/mL) was observed, decreasing slowly afterward (Table 1). The E_2:E_1 ratio (Fig. 2A) consequently increased with rising E_2 levels during the first 12 h from 1 to 5.4 ($p < 0.001$). After 1 week, the mean E_2:E_1 ratio was decreased to 3, reaching values of nearly 2 after 4 weeks, and remained fairly constant at that level (Fig. 2B and Table 1). After 24 weeks, the E_2:E_1 ratio was still significantly increased ($p < 0.05$).

Gonadotrophins

The mean LH value was highest at baseline (17 IU/L), and, 8 h after implantation, a significantly decreased value ($p < 0.001$) of 10 IU/L was observed, remaining stable during the next 4 h (Fig. 3A). At 12 weeks after implantation, the mean LH value reached a minimum level of 6 IU/L (Fig. 3B and Table 1). After 24 weeks, the mean LH value (8 IU/L) was still significantly decreased ($p < 0.05$).

Mean serum profile of FSH was similar to that of LH. A significant decrease of the mean FSH value ($p < 0.05$) was observed from 48 IU/L at baseline to 43 IU/L at 8 h after implantation with a large interindividual variation (Fig. 4A). During follow-up, the mean FSH value decreased further, reaching a lowest value of 17 IU/L at 12 weeks after implantation (Fig. 4B and Table 1). Mean FSH values at most visits were somewhat elevated by a few high individual values. Therefore, all median FSH values were lower, reaching values of 14 IU/L after 12 weeks and decreasing further during the last months until 11 IU/L at 20 and 24 weeks after implantation.

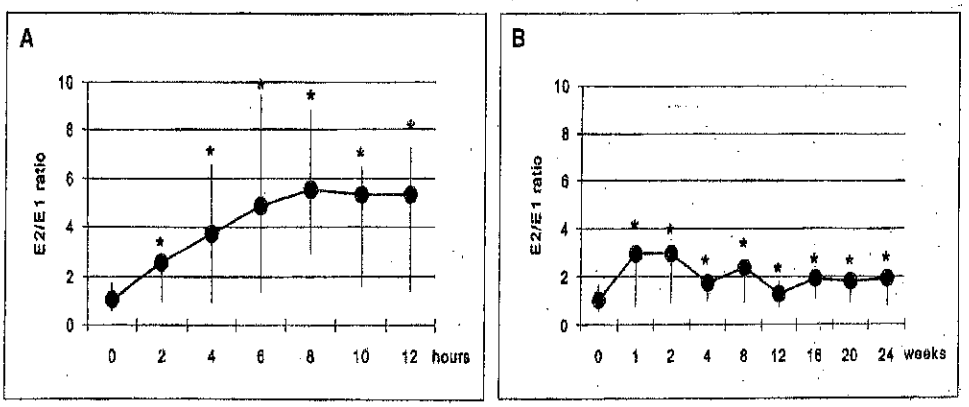

FIG. 2. Mean estradiol:estrone (E_2:E_1) ratio after insertion of one 25-mg E_2 implant (Riselle) in postmenopausal women ($n = 15$) at regular intervals on the day of insertion (A) and at follow-up visits during a period of 24 weeks (B). Vertical lines represent the 25 and 75 percentiles. *, statistically significant change compared with baseline ($p < 0.05$).

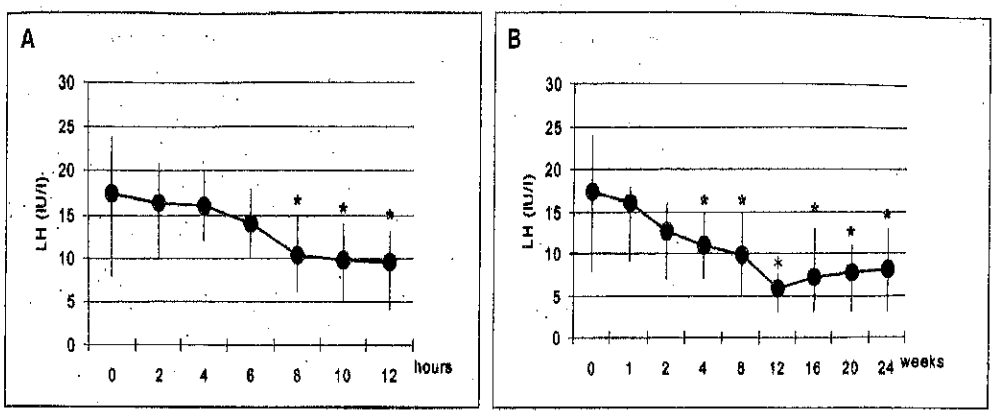

FIG. 3. Mean luteinizing hormone (LH) serum levels after insertion of one 25-mg estradiol (E_2) implant (Riselle) in postmenopausal women ($n = 15$) at regular intervals on the day of insertion (A) and at follow-up visits during a period of 24 weeks (B). Vertical lines represent the 25 and 75 percentiles. *, statistically significant change compared with baseline ($p < 0.05$).

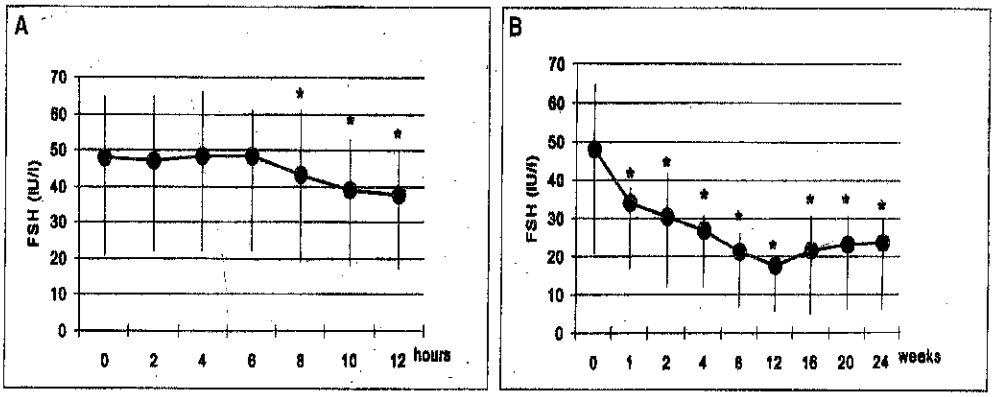

FIG. 4. Mean follicle-stimulating hormone (FSH) serum levels after insertion of one 25-mg estradiol (E_2) implant (Riselle) in postmenopausal women ($n = 15$) at regular intervals on the day of insertion (A) and at follow-up visits during a period of 24 weeks (B). Vertical lines represent the 25 and 75 percentiles. *, statistically significant change compared with baseline ($p < 0.05$).

Climacteric symptoms

The mean scores of all subclasses were significantly decreased ($p < 0.05$) at weeks 8, 16, and 24 (Fig. 5). Vasomotor symptoms completely disappeared in most women. Even after 24 weeks, the reduction in mean symptom score still was 41% for somatic symptoms, 51% for anxiety, 58% for depression and sexual interest, and 84% for vasomotor symptoms. Mean total score of climacteric symptoms was decreased by 64% at week 8 and by 56% after week 24.

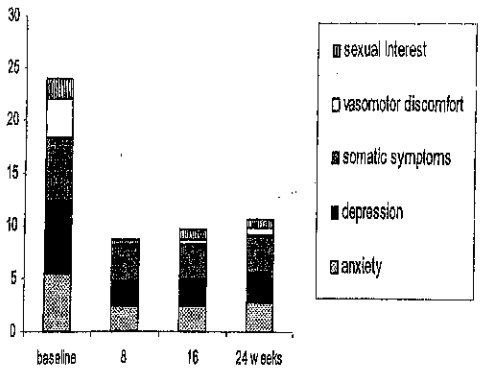

FIG. 5. Climacteric symptoms (Greene climacteric scale) after insertion of one 25-mg estradiol (E_2) implant (Riselle) in postmenopausal women ($n = 15$) during a period of 24 weeks.

Safety

Table 2 represents the effects of E_2 implantation on serum lipids and other metabolic parameters at week 12 and 24. Mean serum values of lipids, glucose, and urea did not show any statistically significant changes. Only serum creatinine was significantly increased at week 12 ($p = 0.03$). However, this increase was not observed at week 24 and was not considered to be of clinical significance.

Mean SHBG values (102 nmol/L at baseline) slightly increased during the first month after implan-

TABLE 2. *Serum lipids and other metabolic parameters after insertion of one 25-mg E_2 implant (Riselle) in postmenopausal women (n = 15) during a period of 24 weeks*

Parameter (mg/dL)	Baseline (mean ± SD)	Week 12 (mean ± SD)	Week 24 (mean ± SD)
Total cholesterol	203.5 ± 31.2	196.4 ± 30.2	191.1 ± 35.4
Triglycerides	146.7 ± 67.9	144.4 ± 106.7	143.1 ± 82.2
HDL cholesterol	48.3 ± 9.9	48.5 ± 11.1	44.2 ± 12.4
LDL cholesterol	136.2 ± 44.2	129.1 ± 30.0	131.5 ± 51.8
Glucose	92.9 ± 13.8	89.1 ± 16.1	91.6 ± 10.1
Urea	31.1 ± 6.6	30.7 ± 10.1	29.0 ± 7.5
Creatinine	0.76 ± 0.09	0.81 ± 0.10[a]	0.79 ± 0.08

E_2, estradiol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Statistically significant change compared with baseline ($p < 0.05$).

tation, reaching levels of 127 nmol/L at week 2 ($p = 0.04$) and 123 nmol/L at week 4 ($p = 0.02$). A gradual return to baseline level was observed at all subsequent follow-up visits.

At week 12, no statistically significant changes were observed in mean values of aspartate aminotranspherase, alanine aminotranspherase, alkaline phosphatase, direct bilirubin, total bilirubin, and total protein. In addition, mean serum levels of AT-III and potassium did not change significantly after 12 weeks. The increase of indirect bilirubin (from 0.66 mg/dL at baseline to 0.77 mg/dL at week 12) reached borderline statistical significance ($p = 0.05$). A statistically significant decrease from baseline to week 12 was found for albumin (from 4.1 to 4.0 g/L; $p = 0.047$) and for sodium (from 140.8 to 137.9 mEq/L; $p = 0.006$). However, none of these changes were considered to be clinically significant.

Blood pressure (systolic and diastolic) and pulse did not show any significant changes during the study period. Mean values measured at all follow-up visits were within normal limits.

Acceptability

Body weight increased from a mean value of 67.4 kg at baseline to a mean value of 69.5 kg at week 20 ($p = 0.003$), reducing to 69.0 kg at week 24 ($p < 0.05$). Mean BMI similarly showed a slight increase from 28.5 kg/m^2 to a maximum value of 29.2 kg/m^2 at week 20 ($p = 0.03$), decreasing to 29.0 kg/m^2 at week 24 ($p = 0.06$). However, waist-to-hip ratio decreased from a mean value of 0.86 at baseline to 0.84 at week 4 and 16 ($p < 0.02$), reaching a value of 0.85 at week 24 ($p < 0.05$).

At the implant site, no abnormalities were detected at any visit. Twelve subjects reported the occurrence of one or more adverse events. In two of them, these adverse events were considered to be related to E_2 treatment: breast pain ($n = 1$) and urethral disorder ($n = 1$). Other side effects, considered to be possibly related to E_2 treatment were headache ($n = 4$), leucorrhea ($n = 4$), ear ache ($n = 3$), breast pain ($n = 2$), urinary infection ($n = 2$), dizziness ($n = 2$), vein pain ($n = 2$), hypertriglyceridemia ($n = 2$), hypercholesterolemia ($n = 1$), nausea ($n = 1$), erythematous rash ($n = 1$), pruritus ($n = 1$), aggravated migraine ($n = 1$), and increased capillary fragility ($n = 1$). All these adverse events were of mild or moderate severity, except for one case of capillary fragility, which was classified as severe. It was not necessary to remove the implant in any of the subjects, implicating 100% compliance.

DISCUSSION

After subcutaneous implantation of a 25-mg E_2 implant (Riselle), E_2 is immediately absorbed into the blood, resulting in a maximum plasma level of almost 70 pg/mL after 10 h, staying above 60 pg/mL during the first week. Thereafter, plasma concentration remains fairly constant until the end of the 24-week study period. This mean steady-state level is within the physiological range of the early follicular phase.[6] In other studies on the pharmacokinetic profile of 25-mg E_2 implants, similar mean plasma levels (ranging from 140 to 330 pmol/L) were observed 6 months after implantation.[7,9,14] Both oral and percutaneous administration of E_2 also provide E_2 levels within this early follicular range.[5,6] E_2 concentrations similar to these steady-state levels of E_2 appeared to be sufficient to relieve climacteric symptoms.[7,9,14] In addition, these E_2 levels were shown to achieve complete calcium homeostasis[19] and to maintain bone mineral density.[9,20]

Peak plasma E_2 levels above the physiological range of 100–1750 pmol/L[21,22] were not observed in this study. Although considerable interindividual variation exists, most women had E_2 levels within the follicular premenopausal range for 6 months. Due to E_2 oxidation in the gastrointestinal tract and in the liver, oral estrogens induce very high E_1 levels, leading to E_2:E_1 ratios

of 1:3–1:5, which are beyond those observed in premenopausal women.[5,6] Subcutaneous administration of E_2 avoids this hepatic first-pass effect and conversion from E_2 to E_1 is thus less extensive as compared with the oral route. In this study, it became evident that subcutaneous administration of E_2 provides an E_2:E_1 ratio of 2:1, which is similar to the premenopausal ratio.[6] This physiological E_2:E_1 ratio also was observed in previous studies on hormonal profiles of E_2 implants.[9,10,14]

The implantation of 25 mg E_2 induces a reduction of gonadotrophin levels to premenopausal levels.[7,9,23] In this study, a similar fall in mean plasma FSH and LH occurred, reaching a lowest mean level after 12 weeks of implantation. All LH values were within the follicular range at 12 weeks or thereafter. FSH values showed a considerable variation between individuals, but more than half of the subjects reached premenopausal FSH levels during the last 3 months of the study period.

Although neither the design nor size of sample in our study were primarily aimed at assessing the effect of E_2 implant on climacteric symptoms, our results are in accordance with the results of other clinical efficacy studies with 20- or 25-mg E_2 implants.[7,8,11,14,15,23] Only one placebo-controlled study has been performed.[8] In this study, the mean overall climacteric score after implantation of 25 mg E_2 was statistically significantly lower compared with placebo. In one study with 20-mg E_2 implants, the duration of action ranged from 4 to 8 months with a duration of 6 months or longer in nearly 75% of the women.[15] In this study, a mean reduction in climacteric score of 56% was still observed after 6 months of implantation. This suggests that most women do not need higher E_2 dosages for control of climacteric symptoms. Moreover, other studies have shown that this 25-mg E_2 implant also adequately prevents bone loss.[9,20,24,25]

A well-established drawback of oral estrogen treatment is the occurrence of a considerable hepatic first-pass effect. This not only leads to a nonphysiological high conversion of E_2 to E_1 but also to marked alterations in hepatic metabolism.[5] Subcutaneous E_2 implantation, on the contrary, does not induce any significant changes in plasma levels of SHBG, hepatic proteins and enzymes, AT-III, and electrolytes. Other studies on the effects of subcutaneous[7–9] or transdermal[5] estrogen therapy also did not report any significant effects on hepatic proteins.

Plasma lipoproteins did not change with the 25-mg E_2 implant treatment. The slight decrease in plasma cholesterol and triglycerides did not reach statistical significance. These results correspond with previous reports on the metabolic effects of 25-mg E_2 implants.[7–9] Depending on dosage, subcutaneous E_2 administration may induce similar favorable changes in plasma lipoproteins as produced by oral estrogen treatment. On the other hand, the rise in plasma triglycerides, observed with oral estrogen therapy and interpreted as potentially unfavorable,[3,4] was not observed with E_2 implants.

No changes were observed in plasma glucose or systolic and diastolic blood pressure. These results are in accordance with a previous study[9] reporting the effects of 25-mg and 50-mg E_2 implants on cardiovascular-related parameters. The use of oral estrogen therapy, however, is associated with an increase in renin substrate (a marker of hepatic action),[5,26,27] which may predispose some women to hypertension.[5,28]

Preliminary data on the implantation procedure with the Riselle implanter indicated that this method was well accepted by both doctors and patients.[29] The needle implantation of the very small 25-mg implant did not induce local irritation, subcutaneous hematoma, or infection in any of the subjects. It was not necessary to remove the implant in any of the subjects in this study. Therefore, 100% patient compliance could be realized.

The increase in mean body weight and BMI observed in this study may be partly attributed to the age-related weight gain after menopause. In two other studies, a similar but nonsignificant increase in body weight was seen during a long-term period of E_2 implant treatment.[9,30] The waist-to-hip ratio, however, was decreased after 6 months. This lower waist-to-hip ratio associated with HRT[31] has a beneficial effect on the cardiovascular risk profile.[31,32]

Side effects were estrogenic in nature. Because of the subcutaneous route and its very low dose (corresponding with a daily dose of approximately 0.15 mg of E_2), nausea, gastrointestinal complaints, and effects on the liver are less likely than with oral estrogens. Skin irritation associated with the transdermal route is also avoided.[4]

It can be concluded that E_2 25-mg implant therapy (Riselle) provides estrogen plasma profiles that are more stable and more physiologic than those obtained by the oral route of administration. In most women, serum E_2 levels remain fairly constant at a level within the physiologic range of the early follicular phase. With the subcutaneous route of administration, the enterohepatic circulation is bypassed, resulting in a less extensive conversion of E_2 to E_1 and avoidance of metabolic disadvantages associated with oral estrogens. This last

feature constitutes an advantage when ERT is required by women suffering from diabetes mellitus, dyslipidemia, hypertension, or obesity.[33] The relatively small amounts of E_2 result in effective relief of climacteric symptoms with minimum occurrence of side effects. Although the effects on bone mass were not studied in this trial, the serum levels obtained are known to offer effective protection against osteoporosis. The needle implantation is convenient with good acceptability and optimal compliance. E_2 implantation is especially suitable for hysterectomized women because the high compliance and convenience of the regimen is not compromised in these women by the necessity of additional progestagen administration to avoid endometrial hyperplasia.

Acknowledgements: We thank Pilar Lara (Social Worker) and Gerardo Cerezo (Laboratory Technician) for their support in the execution of the present study.

The study was partially supported by the Consejo Nacional de Ciencia y Tecnología, Mexico (CONACYT) and by Organon Mexicana.

REFERENCES

1. Grady D, Rubin SM, Petitti DB, et al. Hormone therapy to prevent disease and prolong life in postmenopausal women. *Ann Intern Med* 1992;117:1016–37.
2. Kafonek SD. Postmenopausal hormone replacement therapy and cardiovascular risk reduction: a review. *Drugs* 1994;47(Suppl 2):16–24.
3. Thorneycroft IH. Practical aspects of hormone replacement therapy. *Prog Cardiovasc Dis* 1995;38:243–54.
4. Whitcroft SIJ, Ellirington MC, Whitehead MI. Routes of estrogen administration. In: Asch RH, Studd JWW, eds. *Annual progress in reproductive medicine*. New York: The Parthenon Publishing Group, 1993:235–46.
5. De Lignieres B, Basdevant A, Thomas G, et al. Biological effects of estradiol-17 beta in postmenopausal women: oral versus percutaneous administration. *J Clin Endocrinol Metab* 1986;62:536–41.
6. Powers MS, Schenkel L, Darley PE, Good WR, Balestra JC, Place VA. Pharmacokinetics and pharmacodynamics of transdermal dosage forms of 17 beta-estradiol: comparison with conventional oral estrogens used for hormone replacement. *Am J Obstet Gynecol* 1985;152:1099–106.
7. Lobo RA, March CM, Goebelsmann U, Krauss RM, Mishell DR, Jr. Subdermal estradiol pellets following hysterectomy and oophorectomy: effect upon serum estrone, estradiol, luteinizing hormone, follicle-stimulating hormone, corticosteroid binding globulin-binding capacity, testosterone-estradiol binding globulin-binding capacity, lipids, and hot flushes. *Am J Obstet Gynecol* 1980;138: 714–9.
8. Servy EJ, Bryner JR, Scholer J. Effects of subcutaneous estradiol implants after oophorectomy. *Adv Contr Deliv Syst* 1991;2:1–19.
9. Notelovitz M, Johnston M, Smith S, Kitchens C. Metabolic and hormonal effects of 25-mg and 50-mg 17 beta-estradiol implants in surgically menopausal women. *Obstet Gynecol* 1987;70:749–54.
10. Thom MH, Collins WP, Studd JW. Hormonal profiles in postmenopausal women after therapy with subcutaneous implants. *Br J Obstet Gynaecol* 1981;88:426–33.
11. Stanczyk FZ, Shoupe D, Nunez V, Macias-Gonzales P, Vijod MA, Lobo RA. A randomized comparison of nonoral estradiol delivery in postmenopausal women. *Am J Obstet Gynecol* 1988;159:1540–6.
12. Suhonen SP, Allonen HO, Lahteenmaki P. Sustained-release subdermal estradiol implants: a new alternative in estrogen replacement therapy. *Am J Obstet Gynecol* 1993;169:1248–54.
13. Suhonen S, Sipinen S, Lahteenmaki P, Laine H, Rainio J, Arko H. Postmenopausal oestrogen replacement therapy with subcutaneous oestradiol implants. *Maturitas* 1993;16:123–31.
14. Owen EJ, Siddle NC, McGarrigle HT, Pugh MA. 25 mg oestradiol implants: the dosage of first choice for subcutaneous oestrogen replacement therapy?. *Br J Obstet Gynaecol* 1992;99:671–5.
15. Staland B. Treatment of menopausal oestrogen deficiency symptoms in hysterectomised women by means of 17beta-oestradiol pellet implants. *Acta Obstet Gynecol Scand* 1978;57:281–5.
16. Kuhl H. Pharmacokinetics of oestrogens and progestogens. *Maturitas* 1990;12:171–97.
17. Fotherby K. Intrasubject variability in the pharmacokinetics of ethynyloestradiol. *J Steroid Biochem Mol Biol* 1991;38:733–6.
18. Greene JG. Constructing a standard climacteric scale. *Maturitas* 1998;29:25–31.
19. Selby PL, Peacock M. Dose dependent response of symptoms, pituitary, and bone to transdermal oestrogen in postmenopausal women. *Br Med J (Clin Res Ed)* 1986;293:1337–9.
20. Studd J, Savvas M, Waston N, Garnett T, Fogelman I, Cooper D. The relationship between plasma estradiol and the increase in bone density in postmenopausal women after treatment with subcutaneous hormone implants. *Am J Obstet Gynecol* 1990;163:1474–9.
21. Garnett T, Studd JW, Henderson A, Watson N, Savvas M, Leather A. Hormone implants and tachyphylaxis. *Br J Obstet Gynaecol* 1990;97:917–21.
22. Stumpf PG. Pharmacokinetics of estrogen. *Obstet Gynecol* 1990;75(Suppl 4):9S–17S.
23. van Leusden HA. Comparison of transdermal and subcutaneous administration of estradiol in the treatment of climacteric symptoms [in Dutch]. *Ned Tijdschr Geneeskd* 1987;131:2301–4.
24. Holland EF, Leather AT, Studd JW. The effect of 25-mg percutaneous estradiol implants on the bone mass of postmenopausal women. *Obstet Gynecol* 1994;83:43–6.
25. Naessen T, Persson I, Thor L, Mallmin H, Ljunghall S, Bergstrom R. Maintained bone density at advanced ages after long term treatment with low dose oestradiol implants. *Br J Obstet Gynaecol* 1993; 100:454–9.
26. Geola FL, Frumar AM, Tataryn IV, et al. Biological effects of various doses of conjugated equine estrogens in postmenopausal women. *J Clin Endocrinol Metab* 1980;51:620–5.
27. Elkik F, Gompel A, Mercier-Bodard C, et al. Effects of percutaneous estradiol and conjugated estrogens on the level of plasma proteins and triglycerides in postmenopausal women. *Am J Obstet Gynecol* 1982;143:888–92.
28. Crane MG, Harris JJ, Winsor WD. Hypertension, oral contraceptive agents, and conjugated estrogens. *Ann Intern Med* 1971;74:13–21.
29. Wiegerinck MAHM, Raaymakers L, Moret E, Meuwissen JHJM. Experiences with a new needle system for estradiol implantation [in Dutch]. *Medisch Journaal* 1992;21:222–4.
30. Barlow DH, Abdalla HI, Roberts AD, Al Azzawi F, Leggate I, Hart DM. Long-term hormone implant therapy: hormonal and clinical effects. *Obstet Gynecol* 1986;67:321–5.
31. Kaye SA, Folsom AR, Prineas RJ, Potter JD, Gapstur SM. The association of body fat distribution with lifestyle and reproductive factors in a population study of postmenopausal women. *Int J Obes* 1990;14:583–91.
32. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga P. Waist to hip ratio in middle-aged women: associations with behavioral and psychosocial factors and with changes in cardiovascular risk factors. *Arterioscler Thromb* 1991;11:1250–7.
33. The North American Menopause Society. Consensus opinion: effects of menopause and estrogen replacement therapy or hormone replacement therapy in women with diabetes mellitus. *Menopause* 2000;7:87–93.