Variability of serum estrogens among postmenopausal women treated with the same transdermal estrogen therapy and the effect on androgens and sex hormone binding globulin

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Objective: To examine the variability of serum estrogens in response to transdermal estrogen replacement therapy (ET), and to determine the effects on androgens and sex hormone binding globulin (SHBG).

Setting: Women’s hospital.

Patient(s): Two groups of postmenopausal women: [1] 21 women not on ET enrolled and 17 completed the study; [2] 19 women on continuous transdermal ET enrolled and 13 completed the study.

Intervention(s): Women not on ET were administered a placebo patch or a newly initiated estrogen patch, then crossed over to the alternate treatment. Serum samples were obtained at baseline and the subsequent 3 days from the placebo and new-patch groups and from a separate group of women receiving continuous estrogen patch treatment.

Main Outcome Measure(s): Estradiol (E2), estrone, estrone sulfate, T, dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, free androgen index, and SHBG.

Result(s): There was considerable intrapatient and interpatient variability in the estrogen response to identical treatment doses, with E2 values differing between women as much as 138 pg/mL and E2 increases above baseline differing as much as 90 pg/mL. Continuous treatment increased SHBG and decreased androstenedione levels; however, levels of T, DHEA, DHEAS, and free androgen index, and SHBG did not change.

Conclusion(s): There is great variability of estrogen in response to transdermal ET, but minimal effect on circulating androgens. (Fertil Steril 2003;79:534–42. ©2003 by American Society for Reproductive Medicine.)

Key Words: Estrogen, menopause, variability, androgen, SHBG, estrogen replacement therapy, transdermal

Estrogen affects many human tissues, including cardiovascular, skeletal, breast, central nervous system, urogenital, and uterine tissues (1–6). It has been reported that estrogen replacement therapy (ET) is effective in the treatment of postmenopausal vasomotor symptoms, urogenital atrophy, and osteoporosis. Evidence also supports the role of ET in the prevention of cognitive decline, Alzheimer’s disease, colon cancer, weight gain, and central obesity (7). Past observational, clinical, and basic laboratory research suggests that estrogen is associated with beneficial cardiovascular effects in women (1, 8). Recent randomized controlled trials, however, show that in some women hormone therapy (HT) may exert an early thrombogenic effect and a later antiatherogenic effect (9).

With known beneficial and possible harmful effects of estrogen, the ideal objective of ET would be to administer a medication that would produce levels of estrogen, in each individual woman, adequate to achieve symptom suppression and disease prevention while minimizing unwanted side effects. The optimal range of serum estradiol (E2) for the therapeutic effectiveness of ET has not been established. Some investigators, however, have suggested a ther-
A therapeutic range of E\textsubscript{2} during ET. One investigator reported that a serum E\textsubscript{2} concentration of >60 pg/mL is necessary for prevention of osteoporosis in postmenopausal women (10). Others report 25–45 pg/mL is sufficient for protection of bone (11, 12). It has also been reported that E\textsubscript{2} levels of 60 and 120 pg/mL are necessary for 50% and 100% reduction of hot flashes, respectively (13).

A study carried out in premenopausal female cynomolgus monkeys concluded that endogenous plasma E\textsubscript{2} concentrations of >60 pg/mL were necessary for acetylcholine-mediated dilation of atherosclerotic coronary arteries (14). Others have suggested that a therapeutic range of E\textsubscript{2} between 60 and 150 pg/mL is reasonable, based on existing studies and average plasma E\textsubscript{2} concentrations during the menstrual cycle of 100 pg/mL (10). It is not known, however, whether an attempt to replicate premenopausal hormone levels would result in inappropriately high E\textsubscript{2} concentrations. Some consider E\textsubscript{2} concentrations significantly above 80 pg/mL to be indicative of excessive dosing (15).

It is likely that each woman metabolizes estrogen differently. Many factors such as route of estrogen administration, individual differences in liver function, skin absorption, body composition (fat mass/lean mass), body size, medication interaction, and binding proteins contribute to the different levels of circulating estrogen in the postmenopausal woman.

A number of studies have examined bioavailability or variation in absorption of E\textsubscript{2} in response to ET (16, 17). Most, however, commonly report their findings as descriptive group mean and standard errors. This method of reporting does not depict the true variability of response in each individual. More extensive examination of individual responses to each ET treatment may be required to determine whether variations in response to ET are great enough to be of clinical concern.

Androgens are considered important in cardiovascular disease (18), osteoporosis (19, 20), loss of libido (20, 21), and other conditions in postmenopausal women (22). Oral ET has been reported to decrease endogenous androgens and increase sex hormone binding globulin (SHBG) (23–25). We have recently documented the suppression of dehydroepiandrosterone (DHEA) in young women on oral contraceptive pills and in postmenopausal women on HT (26). A few studies have examined the effect of transdermal estrogen, combined with progestins, on androgens. We are aware of only one study, however, that has examined the effects of transdermal E\textsubscript{2} without progestins, on androgens, and only free testosterone was examined (27).

The purpose of the present study was to determine the hormonal variability in individual patient responses to the same transdermal ET across treatment time starting at baseline in newly initiated and continuous ET. Data were analyzed using several approaches: [1] statistical analysis of variability, [2] analysis of individual data, and [3] comparison of individual values relative to suggested therapeutic ranges and the projected range indicated by the manufacturer. A secondary purpose was to analyze the effects of transdermal ET on adrenal androgens and SHBG at the onset and after continuous ET. This is the first study to carefully determine variability in individual estrogen responses to transdermal ET and examine the individual responses relative to recommended effective levels.

**MATERIALS AND METHODS**

**Study Design**

A randomized, double-blinded, placebo-controlled, crossover design was used to examine the variability of response to newly initiated transdermal ET versus placebo in postmenopausal women. In addition, variability of estrogen response was examined in a separate group of women who had been on continuous ET for a minimum of 9 months. Approval was obtained for this study from the institutional review board of Woman’s Hospital Foundation.

**Experimental Protocol**

A screening visit for all participants included informed consent, demographic information, medical and gynecological history, psychological screening, hematology and serum chemistry, waist/hip ratio, height, and weight. Information collected at the screening visit was used to determine eligibility for the study.

**New and Placebo Estrogen Patch Patients**

Seventeen healthy postmenopausal women who had not been treated with ET for a minimum of 3 months were included in the group to receive a new (N) estrogen patch and a placebo (P) patch in an alternating, crossover fashion. Women in the N and P groups had experienced either natural menopause with no menstruation for at least 12 months (n = 10, 59%), surgical menopause (hysterectomy and bilateral oophorectomy) and were more than 2 months postsurgery (n = 2, 12%), or hysterectomy without oophorectomy performed prior to natural menopause with levels of E\textsubscript{2} <40 pg/mL and follicle stimulating hormone (FSH) >30 IU/L (n = 5, 29%). Women were excluded from the N and P groups if they had any of a number of medical, gynecological, or psychological conditions. Women were also excluded if they were taking any medications that might interfere with the metabolic actions of estrogen for the past 6 weeks.

The N and P group participants were randomized to receive either a newly initiated E\textsubscript{2} patch (N) (36 cm\textsuperscript{2}, Alora, Watson Laboratories, Inc., Corona, CA) for nominal delivery of 0.1 mg of E\textsubscript{2} per day when dosed in a twice weekly regimen, or a placebo patch (P). Fasted serum samples were obtained at baseline followed by the application of the treatment patch to the lower right side of the abdomen. Fasted serum samples were then obtained for an additional 3 con-
secutive days. In addition, samples were taken for 3 more days to observe estrogen decline past the recommended treatment period and to allow the women a more gradual withdrawal from the estrogen patch. Each woman was then given a 1-week washout period before crossing over to the alternate treatment for an additional baseline and 6 days of sampling.

**Continuous Estrogen Patch Patients**

Thirteen different women who had been on ET for at least 9 months before being enrolled in the study comprised the continuous estrogen patch group (C). Five of these women had previously been on oral ET and eight were previously on transdermal ET. All C women were switched from their previous estrogen and placed on twice a week transdermal ET. All C women were switched from their previous patch as those in the N and P groups. The fourth day of the treatment period and to allow the women a more gradual withdrawal from the estrogen patch. Each woman was then given a 1-week washout period before crossing over to the alternate treatment for an additional baseline and 6 days of sampling.

Women in the C group were given the same estrogen patch/placebo patch (n = 16) as those in the N and P groups. Androgen patients Androgen patients

**Androgen Patients**

An age-matched subset of 16 women from the N and P groups and 9 women from the C group was used to examine the effect of transdermal ET on androgens and SHBG. There was no statistically significant difference between androgen subjects groups for age, body mass index (BMI), waste-hip ratio (WHR), or years past menopause (see Table 1). Serum Assays

All baseline and daily serum samples were collected between 0730 and 0830 hours. These samples were allowed to sit at room temperature for 10 minutes and refrigerated for at least 30 minutes to allow for full clotting before centrifuging 10 minutes at 500 × g. Once aliquoted, the specimens were frozen at −80°C until assayed. Steroid hormones were measured by a variety of different RIAs. Estradiol was measured with an ultrasensitive estradiol assay (Third Generation Estradiol, Diagnostic Systems Laboratory, Webster, TX) (28) that uses larger serum volumes, longer incubation time, and changes in antibody concentration to allow measurement of E \(_2\) < 5 pg/mL. The estrone sulfate (E\(_1\)S) assay uses antibodies generated directly against estrone sulfate and allows the direct measurement of E\(_1\)S in serum samples (29).

Estrone (E\(_1\)), T, androstenedione, DHEA, and dehydroepiandrosterone sulfate (DHEAS) were all measured by RIA. All of the reagents were obtained from Diagnostic Systems Laboratory. Sex hormone binding globulin was measured with an IRMA procedure (Diagnostic Systems Laboratory). The intra-assay coefficients of variations for these assays were always <5% and interassay coefficient of variation varied between 6% and 14%. Quality control samples were included in each assay run, and rigid quality control samples were included for each assay. Free androgen index (FAI) was calculated as Testosterone (nmol/L)/SHBG (nmol/L) × 100.

### TABLE 1

Descriptive characteristics of subjects included in the estrogen and androgen studies that were treated with a new estrogen patch, a placebo patch, and a continuous estrogen patch.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estrogen patients</th>
<th>Androgen patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New estrogen patch/placebo patch (n = 13)</td>
<td>Continuous estrogen patch (n = 13)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47 ± 2.6 (35–66)</td>
<td>56 ± 1.4 (47–65)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>26 ± 1.2 (22–28)</td>
<td>24 ± 0.6 (22–27)</td>
</tr>
<tr>
<td>Waist/hip ratio (WHR)</td>
<td>0.83 ± 0.02 (0.73–0.98)</td>
<td>0.80 ± 0.02 (0.73–0.87)</td>
</tr>
<tr>
<td>Years past menopause</td>
<td>10.5 ± 2.1 (1–28)</td>
<td>6.9 ± 1.8 (1–21)</td>
</tr>
</tbody>
</table>

*Note: Values are mean ± SE and (ranges).

*Statistically significant difference between groups. Androgen groups were not statistically significantly different for age, BMI, WHR or years past menopause.

**TABLE 2**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo patch</td>
<td>20 ± 2.8 (7–52)</td>
<td>19 ± 2.3 (7–44)</td>
<td>19 ± 2.0 (8–35)</td>
<td>19 ± 2.2 (7–38)</td>
</tr>
<tr>
<td>New estrogen patch</td>
<td>18 ± 2.1 (8–39)</td>
<td>49 ± 4.7 (23–93)</td>
<td>53 ± 5.8 (26–106)</td>
<td>54 ± 5.7 (25–111)</td>
</tr>
<tr>
<td>Continuous estrogen patch</td>
<td>72 ± 6.5 (49–139)</td>
<td>96 ± 11.1 (49–176)</td>
<td>91 ± 8.1 (64–148)</td>
<td>86 ± 9.4 (58–187)</td>
</tr>
</tbody>
</table>


**RESULTS**

**Group Mean Estrogen Concentrations**

Mean estrogen responses of the three groups revealed that E₂, E₁, and E₁S rose significantly from baseline during N treatment. However, the levels were significantly higher during C treatment as compared to N and P treatments (P<.001; P<.05; P<.001) (Table 2; Figure 1A, B, and C).

**Change Scores and Estradiol Concentrations**

Change of E₂ from baseline was calculated for individuals in each group and revealed a wide range of response. The change from baseline for E₂ during P treatment ranged from 0–8 pg/mL, versus the N treatment range of 14–98 pg/mL and the C treatment range of 0.67–91.00 pg/mL. The maximal (C max ), minimal (C min ), average (C avg ), and change from baseline (C max − C min ) E₂ concentrations are presented in Table 3.

**Individual Variability in the Response to Treatment**

The group mean levels seen in Figure 1 indicate a pattern of transdermal estrogen response typically reported in studies and product descriptions, but examination of our individual patients’ levels reveals a wide range of responses among and within the women. Considerable interpatient and intrapatient variability across days among individual patients is evident during N and C treatment for E₂ (Fig. 2), E₁, and E₁S (data not shown). Some of the women’s hormone levels changed in inconsistent ways during C treatment, showing both increases and decreases over the course of the 4 days of data collection.

To examine individual variability, we created an intrapatient numerical indicator of variability, by calculating a single standard deviation (SD) score for each patient across the 4 days of data collection. Thus, the SD score for each woman reflects her own variability. These SD scores were

**TABLE 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo patch (n = 17)</th>
<th>New estrogen patch (n = 17)</th>
<th>Continuous estrogen patch (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C max (pg/mL)</td>
<td>20 ± 2.3 (8–52)</td>
<td>57 ± 6.1 (27–111)</td>
<td>106 ± 10.6 (65–187)</td>
</tr>
<tr>
<td>C min (pg/mL)</td>
<td>20 ± 2.8 (7–52)</td>
<td>18 ± 2.1 (8–39)</td>
<td>72 ± 6.5 (49–139)</td>
</tr>
<tr>
<td>C max − C min (pg/mL)</td>
<td>−0.004 ± 0.9 (0–8)</td>
<td>39 ± 5.4 (14–98)</td>
<td>33 ± 7.8 (0.67–91)</td>
</tr>
<tr>
<td>C avg (pg/mL)</td>
<td>19 ± 2.1 (8–39)</td>
<td>52 ± 5.2 (25–97)</td>
<td>91 ± 8.8 (57–168)</td>
</tr>
</tbody>
</table>

then averaged for each group (Table 4). For E2, E1, and E1S, we conducted a one-way ANOVA and Tukey post-hoc test to compare variability among treatments. For each hormone, intrapatient variability was lowest in the P group, and was significantly higher with the N and C treatments (E2: P<.001; E1: P<.01; E1S: P<.001). Intrapatient variability was similar and showed no statistically significant difference between the N and C treatments.

There was also considerable interpatient variability across patients in the response to treatment, as indicated by the wide range of E2 concentrations among the patients (see Fig. 2). During N and C treatments, some women’s hormone levels remained stable, others increased slightly, and some increased more dramatically. Estradiol values during N treatment, for example, were found to increase in one woman from a baseline of 8.12 to a peak of 105.91 pg/mL; in another woman, they increased much less, from a baseline of 9.84 pg/mL to a peak of only 27.70 pg/mL during treatment. The ranges of E2 concentration across treatment days are presented in Table 2.

**Therapeutic Range of Estrogen Concentrations**

Our final analysis of the estrogen data focused on the extent to which women had E2 concentrations that fell within a therapeutic range between 60 pg/mL to 150 pg/mL that has previously been suggested in the literature. Baseline and daily E2 values for the women while on the placebo patch ranged from 7–52 pg/mL (see Table 2); therefore, all of the women on P treatment had circulating E2 levels below 60 pg/mL. Analysis of E2 concentrations were not of interest for the N group, because in a clinical setting this is a transient condition until steady-state concentrations are reached.

We examined the number of days that women under C treatment achieved levels between 60 pg/mL to 150 pg/mL (Table 5). On average, women receiving C treatment achieved the lower limit of this therapeutic range (≥60 pg/mL) an average of 3.62 ± 0.24 days out of 4 days. Estradiol levels fell below 60 pg/mL for 28% of women at baseline (day 4 of the previous patch). Women receiving C treatment had levels ≥80 pg/mL on 1.69 ± 0.41 days out of the 4 days of treatment. During C treatment, 77% of the women’s E2 levels fell below 80 pg/mL at baseline (day 4 of the previous patch) and 46% or greater did not have a level ≥80 pg/mL on any treatment day. One woman (8%) main-
tained concentrations of E₂ of ≥100 pg/mL across all 4 treatment days, and 62% did not reach 100 pg/mL on any day. Eighty-five percent did not reach 150 pg/mL on any day, and no woman maintained ≥150 pg/mL across all 4 treatment days.

Androgens

An age-matched subset of the women in each group (see Table 1) was used to determine androgen responses to treatment. The estrogen data for this subset was essentially the same as the data from the full groups. Treatments were compared for serum levels of T, androstenedione, DHEA, and DHEAS, as well as for SHBG and FAI, using separate 3 × 3 treatment × days (time) ANOVAs with repeated measures on the second factor with Tukey post-hoc follow-up analyses where required. Baseline levels of T, androstenedione, DHEA, DHEAS, and SHBG, as well as FAI are shown in Table 6. There were no statistically significant changes over the 3 days of analysis (P > .10) nor any statistically significant differences between groups (P > .10) for T, DHEA, DHEAS, and FAI (data not shown). Androstenedione levels were unchanged throughout the study in the P and N groups, but decreased from baseline to day 3 in the C group (data not shown). Analysis of these data indicated a statistically significant group by days’ interaction (P < .05). Follow-up analysis comparing groups at each time point indicated the C treatment values were significantly lower than the P and N treatment values only on day 3. A statistically significant group difference (P < .001) was seen for SHBG, as the values were higher with C treatment than the other two treatments (data not shown).

DISCUSSION

In the present study, we have used a randomized, double-blind, crossover design to examine daily serum estrogen

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**Table 5**

Percentage of continuous estrogen patch users who achieved recommended range of estradiol across treatment days.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (Day 4)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 13)</td>
<td>(n = 13)</td>
<td>(n = 13)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>E₂ ≥ 60 pg/mL</td>
<td>72% (10)</td>
<td>92% (12)</td>
<td>100% (13)</td>
<td>92% (12)</td>
</tr>
<tr>
<td>E₂ ≥ 80 pg/mL</td>
<td>23% (3)</td>
<td>54% (7)</td>
<td>46% (6)</td>
<td>46% (6)</td>
</tr>
<tr>
<td>E₂ ≥ 100 pg/mL</td>
<td>8% (1)</td>
<td>31% (4)</td>
<td>31% (4)</td>
<td>15% (2)</td>
</tr>
<tr>
<td>E₂ ≥ 150 pg/mL</td>
<td>0% (0)</td>
<td>15% (2)</td>
<td>0% (0)</td>
<td>8% (1)</td>
</tr>
</tbody>
</table>

*Note: Values are percent (number).*

levels in women (who were previously not on ET) during treatment of a newly initiated 0.1 mg estradiol patch and a placebo patch. In addition, serum levels of estrogens were studied in a separate group of women who had been treated with ET continually for many months. The ET dose remained constant for all women while the daily E2, E1, and E1S levels. Intrapatient and interpatient variability were determined.

**Baseline Estrogen Levels**

We have used an ultrasensitive estradiol assay that allowed us to detect serum levels in the postmenopausal patient below the assay sensitivity of most commercially available methods (28). Baseline endogenous E2 levels, before any treatment, of women in the P and N groups ranged from 7.45 to 52.05 pg/mL, indicating a wide variability of endogenous E2 among postmenopausal women not taking hormones. Increasing adiposity was associated with greater endogenous baseline E2 levels. The women with higher baseline E2 levels had the highest BMI, and the women with a lower BMI had lower baseline E2 levels. Consideration of baseline values of postmenopausal women may be important in deciding preparation and dosage when first initiating ET.

**Mean Estrogen Levels and Variability of Estrogen Response**

Mean values for E2, E1, and E1S were lowest during P treatment, more elevated during N treatment, and highest during C treatment. Even though transdermal estrogen administration eliminates the first-pass effect of the liver, E1 and E1S were both elevated with transdermal estrogen treatment in this study, demonstrating a hepatic role in the metabolism of estrogens administered by the transdermal route. Mean E2 values for the N and C groups (see Fig. 1) demonstrate a rise from baseline, and relatively stable values for the remaining treatment days.

When the participants’ results were viewed individually, however (see Fig. 2), a dramatic interpatient variability was observed in the N and C groups; some women had E2 increases from baseline less than 1 pg/mL, and others had E2 increases from baseline as great as 98 pg/mL (see Table 3). A single E2 measurement, after several weeks of treatment, may detect women who respond poorly to treatment and remain at lower E2 levels. Despite their already elevated E2 levels from continuous estrogen therapy, considerable interpatient variability also was observed with the study-patch treatment in the C group. The range of E2 increase above baseline between women in the C group was 0.67 to 91 pg/mL. In addition, intrapatient variability was observed in several women during C treatment, whose estrogen levels were unstable, increasing and decreasing in an inconsistent manner over the treatment days (see Fig. 2). The nature of this individual variability is not indicated by the manufacturers of ET treatments, nor are they reported in most ET studies. Rather, mean values are presented that mask the true nature of serum E2 levels in individual patients. The clinical significance of this estrogen variability may be unappreciated.

Although we found considerable variability with transdermal ET, it should be noted that oral preparations appear to produce even greater variability than transdermal treatments (30). Menopause symptoms can be induced by low levels of estrogen, as well as by how rapidly estrogen levels fall. Daily changes in estrogen levels seen in the present study may explain the fluctuations of symptoms seen in some women while they are on ET. However, it should be noted that not all women are symptomatic, even with low E2 levels.

In N treatment group, E2 levels remained elevated above baseline during the first 4 days, the suggested duration of patch use, and remained above baseline through the sixth day. Higher E3 in the C group, compared with the N group, may be related to estrogen-induced changes in metabolism or increases in SHBG, which may sequester and delay the disappearance of estrogen from the circulation.

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TABLE 6

Baseline concentrations of testosterone, androstenedione, dehydroepiandrosterone, dehydroepiandrosterone sulfate, and sex hormone binding globulin, as well as free androgen index for placebo patch, new estrogen patch, and continuous estrogen patch treatments.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo patch (n = 16)</th>
<th>New estrogen patch (n = 16)</th>
<th>Continuous estrogen patch (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>0.24 (0.05)</td>
<td>0.28 (0.04)</td>
<td>0.28 (0.03)</td>
</tr>
<tr>
<td>Androstenedione</td>
<td>0.76 (0.07)</td>
<td>0.76 (0.06)</td>
<td>0.70 (0.11)</td>
</tr>
<tr>
<td>Dehydroepiandrosterone</td>
<td>4.65 (0.67)</td>
<td>4.70 (0.77)</td>
<td>7.47 (2.64)</td>
</tr>
<tr>
<td>Dehydroepiandrosterone sulfate</td>
<td>62.63 (7.18)</td>
<td>54.61 (9.19)</td>
<td>61.58 (13.99)</td>
</tr>
<tr>
<td>Sex hormone binding globulin</td>
<td>68.26 (12.24)</td>
<td>67.42 (12.52)</td>
<td>157.66 (23.87)</td>
</tr>
<tr>
<td>Free androgen index</td>
<td>1.61 (0.37)</td>
<td>2.16 (0.37)</td>
<td>0.93 (0.50)</td>
</tr>
</tbody>
</table>

Note: Values are means (± SE).

Therapeutic Range of Estrogen Concentrations

Use of the transdermal estrogen patch attempts to maintain tonic levels characteristic of the early to middle follicular phase (16, 31); however, in some women the serum E2 levels are both above and below the manufacturer’s projected range of 70 to 100 pg/mL. (35) and above and below a previously suggested treatment range of 60–150 pg/mL. If the upper limit of the previously suggested therapeutic range (150 pg/mL) is necessary for disease protection, 15% of women achieved that level and only on the first day of treatment. If a more conservative upper limit of 80 pg/mL is used, 54% or less of women achieved that level on any given day of treatment. More research is needed to investigate variability in response to ET with other preparations, as well as the reason for daily fluctuation in estrogen levels and its impact on treatment effectiveness.

Androgen Response

The importance of androgens in the postmenopausal patient is increasingly recognized, and in the past few years many clinicians have added some form of androgen to ET regimens, particularly in those patients who have been oophorectomized and have lower serum testosterone levels (32). We are aware of only one study that has examined the effect of transdermal estrogens without progestins, on androgens, and only free testosterone was examined (27). Testosterone levels in the postmenopausal patient have been reported to be relatively unchanged (33) or slightly lower than in premenopausal women. A recent suggestion that the postmenopausal ovary does not produce T (34) has further confused the understanding of androgens in the postmenopausal woman.

Studies with oral ET administration have indicated a decrease in serum androgens due to either changes in SHBG or a direct effect on adrenal androgen production (23–25). Given this information, we considered it important to determine whether the transdermal estrogen used in this study has any effect on circulating androgen levels. Serin et al. (27) reported no change in free T or SHBG levels after transdermal ET. However, with prolonged ET (the C group) in the present study, an increase in SHBG was evident. This may be due to higher estrogen levels over time and the slow response of SHBG to increased estrogen. Despite an increase in SHBG and estrogen levels, the transdermal ET used in this study had no statistically significant effect on T, DHEA, DHEAS, and FAI. This may be due to the lower physiological levels of estrogens seen with the transdermal route.

Androstenedione concentrations mirrored mean E2 response patterns in the same women. Androstenedione concentrations decreased and reached statistical significance on treatment day 3. Adrenal cortical expression of androstenedione may be more acutely sensitive to circulating E2 than the other androgens which would account for the significant decline on the third day. Further investigation of the cause and effect of this reduction in androstenedione is warranted. It seems of clinical importance to know whether an estrogen treatment has a major impact on serum androgen levels.

CONCLUSIONS

In summary, these studies demonstrate an unexpected degree of interpatient and intrapatient variability in women using a transdermal estrogen patch for ET. The variability is such that estrogen levels in some patients drastically climb above or fall below the pharmacologic range described by the manufacturer as well as that previously suggested therapeutic ranges. Monitoring of E2 levels in patients using transdermal E2 to determine the individual response of estrogen may be of clinical importance. Corresponding changes in dosing may be appropriate for extremes in circulating estrogen levels.

The transdermal ET used in this study increased the levels of SHBG, decreased androstenedione, but had no statistically significant effect on testosterone, DHEA, DHEAS, or FAI. Future studies should examine variable responses to other forms of ET. Additionally, long-term studies are needed to determine whether a therapeutic range of estrogen is necessary for protection from diseases affected by estrogen.

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