Different Effects of Transdermal and Oral Hormone Replacement Therapy on the Renin-Angiotensin System, Plasma Bradykinin Level, and Blood Pressure of Normotensive Postmenopausal Women

Junko Ichikawa, Hiroyuki Sumino, Shuichi Ichikawa, and Makoto Ozaki

Background: This study compared the efficacy of transdermally administered estradiol with that of orally administered conjugated equine estrogens (CEE) on the renin–angiotensin system, plasma bradykinin level, and blood pressure (BP) in normotensive postmenopausal women (PMW).

Methods: A total of 38 normotensive PMW were randomly assigned to two groups. The transdermal hormone replacement therapy (HRT) group consisted of 19 women treated with a continuous transdermal estradiol patch (36 μg/day) plus cyclic oral medroxyprogesterone acetate (MPA; 2.5 mg/day for 12 days) for 12 months. The oral HRT group consisted of 19 women who received continuous oral CEE (0.625 mg/day) plus cyclic oral MPA (2.5 mg/day for 12 days) for 12 months. Plasma renin activity (PRA), serum angiotensin-converting enzyme (ACE) activity, plasma angiotensin (Ang) I, Ang II, and bradykinin concentrations, and BP were measured before and 12 months after the start of HRT.

Results: Transdermal HRT significantly decreased both diastolic and mean BP and concomitantly reduced bradykinin levels (all \( P < .05 \)). However, no significant changes in PRA, ACE activity, Ang I, or Ang II levels were observed. The BP remained unchanged in the oral HRT group, but the PRA, Ang I, Ang II, and bradykinin levels had significantly increased and ACE activity had significantly decreased (all \( P < .05 \)) at 12 months after the start of HRT.

Conclusions: Transdermal HRT decreased BP in normotensive PMW without influencing Ang II, whereas oral HRT increased Ang II without altering BP. Transdermal HRT may be more beneficial than oral HRT with regard to BP and Ang II levels. Am J Hypertens 2006;19:744–749 © 2006 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, bradykinin, estrogen, renin–angiotensin system, postmenopausal women.

The renin–angiotensin system plays a critical role in the regulation of blood pressure (BP) and in the pathophysiology of hypertension. Oral hormone replacement therapy (HRT) dose-dependently increases renin substrate, which is the same as angiotensinogen, but transdermal HRT usually does not affect angiotensinogen levels.1–3 Plasma renin activity (PRA) has been found to be either unchanged or increased in women who receive either oral or transdermal HRT.4–7 Oral HRT reduces the activity of angiotensin-converting enzyme (ACE) in postmenopausal women, whereas transdermal HRT has little effect.2,4,8–11 Generally, the reduction in ACE activity would be expected to reduce the plasma angiotensin (Ang) II levels and to increase the Ang I and bradykinin levels. In fact, however, the plasma Ang I levels were either unchanged or increased by oral HRT, whereas the plasma Ang II levels were increased.4 The bradykinin levels increased concomitantly as ACE activity decreased in the women who received oral HRT.4,5,9,10 However, whether transdermal HRT, like oral HRT, affects circulating levels of Ang I, Ang II, and bradykinin in postmenopausal women has not been investigated.

In contrast to oral HRT, transdermal HRT has been reported to have little effect on serum lipids, lipoprotein, and fibrinolysis12,13 and to have no adverse effects on coagulation, renin substrate, or triglyceride levels.12,14 Af-
ter oral administration, most estrogens reach the liver via the portal circulation and are metabolized through a process called the first-pass effect. The result is nonphysiologic levels of estrone, estrone sulfate, and various hepatic proteins such as renin substrate, sex-hormone-binding globulin, thyroxine-binding globulin, and cortisol-binding globulin. As parenteral estradiol administration avoids hepatic metabolism, it may prevent some of the undesired effects of oral treatment and be more suitable for HRT.15,16 It therefore seemed important to investigate the physiologic effects of estrogen administered by both transdermal and oral routes.

This study was designed to compare the effects of transdermal and oral HRT on components of the renin-angiotensin system, plasma bradykinin levels, and BP in normotensive postmenopausal women.

Methods

Subjects

A total of 38 healthy normotensive Japanese postmenopausal women (mean age 55.1 ± 6.9 years, range 47 to 71 years) with no evidence of gynecologic disorders volunteered to participate in this study. Each of the subjects had experienced a natural menopause that had lasted for >1 year. Menopausal status was confirmed by a serum estradiol (E2) concentration <20 pg/mL and a serum follicle-stimulating hormone (FSH) concentration >40 mIU/mL. None of the subjects had smoked or received hormonal therapy before enrollment or had any contraindications to such therapy. Before entering the study, each subject underwent physical and laboratory examinations, including a gynecologic evaluation, mammography, 12-lead electrocardiography, and echocardiography. Women with any of the following disorders were excluded: diabetes mellitus, hypertension, thyroid disease, acute or severe chronic liver disease, heart failure, renal failure, thromboembolic or ischemic cardiac disease, breast or endometrial cancer, a personal or family history of breast cancer, or unexplained ischemic cardiac disease, heart failure, renal failure, thromboembolic or ischemic cardiac disease, breast or endometrial cancer, a personal or family history of breast cancer, or unexplained vaginal bleeding. All of the subjects had a normal BP and had no previous history of angina pectoris or an episode of myocardial infarction. The subjects were free from arterial hypertension, thyroid disease, acute or severe chronic liver disease, heart failure, renal failure, thromboembolic or ischemic cardiac disease, breast or endometrial cancer, a personal or family history of breast cancer, or unexplained vaginal bleeding. None of the subjects had smoked or received hormonal therapy before enrollment or had any contraindications to such therapy.

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Physical Examination

After collecting the blood samples, the subjects were allowed to rest for at least 30 min before measuring BP and pulse rate. The BP in the subject’s right arm was measured three times using a mercury sphygmomanometer, and the mean of the three measurements was recorded. Anthropometric characteristics were then determined. Weight was measured to the nearest 0.1 kg, and height was measured to the nearest 0.5 cm. Body mass index was also calculated.

Assays

Serum total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol concentrations were determined using enzymatic methods (Medca Japan, Konosu, Japan). The serum high-density lipoprotein (HDL) cholesterol concentration was determined electrophoretically using an HDL Cholesterol Supply Kit (Helena Laboratory, Beaumont, TX). Serum FSH and E2 concentrations were measured by radioimmunoassay using commercially available kits (Boehringer Mannheim, Germany). The PRA was determined by radioimmunoassay as previously reported.4 Both Ang I and Ang II were quantitated by radioimmunoassay according to the original methods devised by SRL, Inc. (Tokyo, Japan).17 The normal range for Ang I values is <110 pg/mL, and the normal range for Ang II values is <22 pg/mL. After mixing the sample with assay buffer (Tris buffer) containing 100 μL of tracer (125I-Ang I or Ang II) and 100 μL of the primary antibody to Ang I or Ang II, the sample was incubated for 18 to 24 h at 2° to 8°C. A 100-μL volume of the secondary antibody was then added, and the mixture was incubated for an additional 1 h at 2° to 8°C. After centrifugation at 3500 rpm for 20 min at 2° to 8°C, the supernatant was decanted and radioactivity was measured. Both Ang I and Ang II levels were determined by extrapolation from standard curves. The plasma bradykinin concentration was measured by a
radioimmunoassay, as previously reported. Serum ACE activity was determined by colorimetry according to the method of Kasahara and Ashihara.

**Statistical Analysis**

Data are reported as mean ± SD. One-way analysis of variance (ANOVA) and the Scheffé F test were used to compare the clinical characteristics of the two groups. Two-way ANOVA for repeated measures was used to analyze the differences between values recorded at baseline and at 12 months. All probability values were two-tailed. A value of \( P < .05 \) was considered statistically significant. All statistical analyses were performed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL).

**Results**

The characteristics of the study population are listed in Table 1. Before HRT, no significant differences with regard to age, body mass index, total cholesterol, triglyceride, HDL cholesterol, or LDL cholesterol were observed between the two groups.

The changes in body mass index, BP, pulse rate, and hormone levels, including FSH, estradiol, renin–angiotensin system, and bradykinin, after 1 year of HRT are listed in Tables 2 and 3. Body mass index, BP, pulse rate, FSH, estradiol, PRA, ACE activity, Ang I, Ang II, and bradykinin levels at baseline and at 12 months after the start of HRT were similar in the two groups. Body mass index did not change during the study. In the transdermal HRT group, DBP and mean BP were significantly lower after 12 months of HRT (\( P < .05 \)), but SBP and pulse rate were not. In the oral HRT group, BP and pulse rate did not change during the study. The HRT was associated with a significant increase in the E2 concentration (\( P < .01 \)) and a decrease in the FSH level (\( P < .01 \)) in both groups, confirming patient compliance with the regimen. In the transdermal HRT group, the PRA, Ang I, Ang II, and ACE activity levels showed no significant changes, but the bradykinin level decreased (\( P < .05 \)). By contrast, at 12 months after the start of HRT, the oral HRT group showed significant increases in PRA, Ang I, Ang II, and bradykinin values (all \( P < .01 \)) and a significant decrease in ACE activity (\( P < .01 \)).

**Table 1. Characteristics at baseline in the two treatment groups**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Transdermal HRT group</th>
<th>Oral HRT group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Age (y)</td>
<td>54.6 ± 7.6</td>
<td>55.5 ± 6.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>20.8 ± 2.3</td>
<td>22.2 ± 2.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>206.0 ± 28.9</td>
<td>210.5 ± 29.9</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>89.0 ± 38.5</td>
<td>87.1 ± 34.4</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>59.8 ± 11.1</td>
<td>55.1 ± 12.0</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>130.1 ± 30.4</td>
<td>134.7 ± 27.6</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; HRT = hormone replacement therapy; LDL = low-density lipoprotein.

All data are shown as mean ± SD.

**Table 2. Changes in blood pressure, pulse rate, and hormone levels, including follicle-stimulating hormone and estradiol, after 1 year of hormone replacement therapy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transdermal HRT</th>
<th>Oral HRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>119.7 ± 13.9</td>
<td>117.4 ± 16.1</td>
</tr>
<tr>
<td>12 months</td>
<td>116.4 ± 13.9</td>
<td>115.9 ± 15.9</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>75.8 ± 8.7</td>
<td>73.3 ± 11.5</td>
</tr>
<tr>
<td>12 months</td>
<td>72.7 ± 6.6</td>
<td>74.0 ± 13.0</td>
</tr>
<tr>
<td>Mean BP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>90.5 ± 10.2</td>
<td>87.9 ± 12.5</td>
</tr>
<tr>
<td>12 months</td>
<td>87.3 ± 8.1</td>
<td>87.9 ± 13.7</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>64.4 ± 5.8</td>
<td>61.7 ± 4.7</td>
</tr>
<tr>
<td>12 months</td>
<td>63.8 ± 4.1</td>
<td>62.1 ± 4.7</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62.7 ± 27.5</td>
<td>64.8 ± 23.8</td>
</tr>
<tr>
<td>12 months</td>
<td>27.9 ± 13.2</td>
<td>30.2 ± 20.9</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.8 ± 53.3</td>
<td>15.1 ± 73.0</td>
</tr>
<tr>
<td>12 months</td>
<td>91.3 ± 74.9</td>
<td>73.0 ± 34.9</td>
</tr>
</tbody>
</table>

BP = blood pressure; DBP = diastolic blood pressure; FSH = follicle-stimulating hormone; HRT = hormone replacement therapy; SBP = systolic blood pressure.

All data are shown as mean ± SD.

**Discussion**

This study was designed to compare the efficacy of transdermally administered E2 and orally administered conjugated equine estrogens on the renin–angiotensin system of normotensive postmenopausal women.

Consistent with the other findings, transdermal HRT did not significantly influence PRA or ACE activity. Seely et al. and Faguer de Moustier et al. also demonstrated that transdermal E2 had no effect on PRA in postmenopausal women, and Proudler et al. reported no significant changes in PRA or ACE activity as a result of transdermal E2 therapy. In addition, the present study showed that transdermal HRT had no impact on the plasma Ang I or Ang II levels.
of normotensive postmenopausal women. These findings may reflect the fact that transdermal HRT did not affect PRA and ACE activity.

Despite our results showing that transdermal HRT did not significantly influence the renin–angiotensin system, transdermal HRT did reduce DBP, mean BP, and the plasma bradykinin concentration. Based on the results of 24-h ambulatory BP monitoring, Akkad et al. reported significant decreases in night-time SBP and DBP and daytime DBP after transdermal HRT in normotensive postmenopausal women but no significant BP changes after oral HRT. Vongpatanasin et al. also reported that transdermal HRT significantly reduced the mean 24-h DBP in normotensive postmenopausal women whereas oral HRT did not. The findings in these studies corroborate the present results. Although the mechanisms by which transdermal HRT decreases BP and plasma bradykinin in postmenopausal women are unclear, several mechanisms have been speculated. Chronic transdermal HRT has been shown to activate the vasodilator process mediated by nitric oxide or prostacyclin and to decrease sympathetic activity in postmenopausal women.

This in turn leads to the down-regulation of Ang II type 1 receptor mRNA and tissue ACE activity after the subcutaneous administration of estradiol to ovariectomized rats. The fact that estrogen attenuates Ang type 1 receptor expression in vivo has also been revealed by PET studies. Furthermore, the administration of candesartan to normotensive postmeno-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Transdermal</th>
<th>Oral</th>
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<tbody>
<tr>
<td>PRA (ng/mL/h)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>0.7 ± 0.8</td>
<td>0.5 ± 0.3</td>
</tr>
<tr>
<td>12 months</td>
<td>0.6 ± 0.5</td>
<td>1.0 ± 0.9*</td>
</tr>
<tr>
<td>ACE activity (IU/L)</td>
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</tr>
<tr>
<td>Baseline</td>
<td>13.5 ± 5.2</td>
<td>16.3 ± 3.9</td>
</tr>
<tr>
<td>12 months</td>
<td>12.9 ± 4.7</td>
<td>13.9 ± 3.8</td>
</tr>
<tr>
<td>Angiotensin I (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>48.4 ± 29.2</td>
<td>79.7 ± 83.0</td>
</tr>
<tr>
<td>12 months</td>
<td>36.7 ± 15.1</td>
<td>237.4 ± 81.4*</td>
</tr>
<tr>
<td>Angiotensin II (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>14.0 ± 8.3</td>
<td>11.7 ± 4.3</td>
</tr>
<tr>
<td>12 months</td>
<td>14.4 ± 11.7</td>
<td>22.8 ± 9.5</td>
</tr>
<tr>
<td>Bradykinin (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.9 ± 11.7</td>
<td>23.0 ± 15.4</td>
</tr>
<tr>
<td>12 months</td>
<td>21.9 ± 9.3</td>
<td>72.1 ± 78.9*</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; PRA = plasma renin activity. All data are shown as mean ± SD.

* P < .01 v transdermal group (ANOVA).

The results of the Heart and Estrogen/progestin Replacement Study (HERS) showed an increased incidence of coronary heart disease during the first year after menopause in women with established coronary disease, and the results of other studies, including the Women’s Health Initiative (WHI) study, have confirmed that HRT should not be used for the primary prevention of coronary heart disease. These negative results were found in subjects receiving oral HRT. Thus it seems important to investigate the physiologic effects of estrogen administered by the transdermal route compared with the oral route. In the present study, oral HRT increased plasma Ang II but transdermal HRT did not. The renin–angiotensin system, specifically Ang II, plays a critical role in the pathophysiology of hypertension, cardiac hypertrophy, congestive heart failure, and coronary heart disease. The binding of Ang II to Ang II type-1 receptors produces pathophysiologic effects such as cell growth, nephrosclerosis, vascular media hypertrophy, endothelial damage, neointima formation, and processes leading to atherothrombosis. Because the inhibition of ACE or the blockade of Ang II type-1 receptors improved cardiovascular outcome in a large clinical trial, our results seem to suggest that the neutral effect of transdermal HRT on the renin–angiotensin system might be a safer method of treatment for postmenopausal women. Transdermal HRT decreased DBP and mean BP in normotensive postmenopausal women, whereas oral HRT did not. Even small reductions in DBP in normotensive populations have been postulated to decrease the risk of future coronary heart disease or stroke by...
5% to 10%. This indicates that transdermal HRT may be effective for reducing the risk of future cardiovascular disease in normotensive postmenopausal women. Thus large prospective studies are necessary to establish the effect of transdermal HRT on coronary heart disease.

This study has some limitations. Irreversible cryoactivation of prorenin to renin occurs when blood is chilled for centrifugation before freezing. Cryoactivation may have accounted for the relatively large variance in the PRA data. This phenomenon may have obscured differences in the renin level that may have been present in the transdermal group, although the lack of an increase in Ang I and Ang II in the transdermal group may suggest that significant cryoactivation is unlikely to have occurred. Unfortunately renin substrate was not measured in the present study. Renin substrate likely increased in the oral group and may be responsible for the increase in renin system activity.

In conclusion, the results of this study showed that transdermal HRT decreased DBP, mean BP, and the plasma bradykinin concentration in normotensive postmenopausal women without influencing components of the renin–angiotensin system. In contrast oral HRT increased PRA, Ang I, Ang II, and bradykinin, and decreased ACE activity without altering BP. Transdermal HRT, rather than oral HRT, may be beneficial with regard to BP and Ang II levels.

Acknowledgments
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