

Renin Substrate Levels Decrease With Transdermal HT and Increase With Oral HT

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ABSTRACT

OBJECTIVE: While there are many physiological differences between the transdermal patch and oral routes of delivery for hormone therapy (HT), this study analyzed the changes in plasma renin substrate (RS) or angiotensinogen levels in postmenopausal women on CombiPatch[®] transdermal patch HT (50 µg 17β-estradiol [E₂]/140 µg norethindrone acetate [NETA]) vs Prempro[™] oral HT (0.625 mg conjugated equine estrogens [CEE]/2.5 mg medroxyprogesterone acetate [MPA]) during a 20-week trial.

DESIGN: This randomized, double-blind, double-dummy, parallel treatment-group, multicenter trial involved 186 women, 1 to 6 years postmenopausal. After a 4-week placebo run-in phase, patients were randomized to 1 of 2 treatment arms for 20 weeks: CombiPatch + placebo capsule or Prempro capsule + placebo patch.

RESULTS: At the pretreatment visit, there was no significant difference in RS levels between the 2 treatment groups ($P=0.636$), but at weeks 12 and 20, patients on CombiPatch had significantly lower RS levels compared to women receiving Prempro ($P<0.001$ at both visits). A significant reduction in RS was observed within the CombiPatch arm from the pretreatment visit to week 12 ($P<0.001$) and week 20 ($P<0.001$). Within the Prempro treatment arm, a significant increase in RS was noted from the pretreatment visit to week 12 ($P<0.001$) and week 20 ($P<0.001$).

CONCLUSION: Angiotensinogen (RS), a circulating α-globulin made in the liver, is increased compared to baseline after 20 weeks of treatment with Prempro but decreased compared to baseline after 20 weeks of treatment with CombiPatch. Angiotensinogen is a precursor substrate of the renin-angiotensin-aldosterone system (RAAS) and has been implicated in the development of hypertension. However, further studies need to be conducted to demonstrate the effect of transdermal patch therapies on hypertension.

INTRODUCTION

- Elevations in blood pressure are not associated with transdermal estrogens, either alone or in combination with progestins,¹⁻³ whereas results with oral HT are variable.^{1,2}
- Angiotensinogen or RS is a circulating α-globulin, produced by the liver and activated by renin from the kidney, which activates the RAAS. Activation of RAAS can lead to increased blood pressure.⁴
- RS increases with oral therapy, but transdermal therapy has a lower impact on angiotensinogen generation.^{5,6}

CombiPatch is a registered trademark of Novogyne Pharmaceuticals. Prempro is a trademark of Wyeth Pharmaceuticals.

TABLE 1. Demographic Characteristics

Demographic Characteristics	CombiPatch (n=92)	Prempro (n=94)	P-value
Age (y; mean ± SD)	51.9 ± 4.2	52.5 ± 4.7	0.340
Race [n (%)]			
Caucasian	81 (88)	83 (88)	0.760
African American	3 (3.3)	6 (6.4)	
Asian	2 (2.2)	1 (1.1)	
Hispanic	5 (5.4)	4 (4.3)	
Other	1 (1.1)	0 (0.0)	
Weight (lbs; mean ± SD)	162.9 ± 32.8	159.5 ± 29.4	0.467
Height (in.; mean ± SD)	64.4 ± 2.2	64.3 ± 2.5	0.848
Age at menopause	48.8 ± 4.0	49.3 ± 3.8	0.336
Time since menopause (y; mean ± SD)	3.1 ± 2.4	3.2 ± 3.0	0.834
Pretreatment renin substrate levels (ng/mL)	2457.8	2557.6	0.636

Demographic characteristics were analyzed by a 2-sample t-test, except for race, which was analyzed by a 2-tailed Fisher's Exact test.

- Observed differences in the effects of transdermal patch and oral therapies on RS may be due to the fact that transdermal patch therapy bypasses first-pass liver metabolism, while oral therapy undergoes first-pass liver metabolism, making transdermal patch therapy a more favorable clinical option.

- Exclusion criteria included: undiagnosed menstrual bleeding within past 12 months; diagnosis of current endometrial hyperplasia; diagnosis of past or current malignancies or medical conditions for which HT is contraindicated; uncontrolled hypertension; active coagulopathy, thrombophlebitis, or thromboembolic disorders; serum chemistry AST or ALT greater than 2 times normal or creatine ≥ 2 mg/dL; history of alcohol or drug abuse in the past 12 months; presence of any active dermatological disease that could modify skin absorption of study drug; participation in any investigational drug study within 30 days prior to screening; and known hypersensitivity to estrogen, progestin, or to CombiPatch or Prempro ingredients.

OBJECTIVE

- To compare changes in plasma RS levels in postmenopausal women on transdermal (CombiPatch) vs oral HT (Prempro) during a 20-week trial.

PATIENTS & METHODS

Study Design

- This was a randomized, double-blind, double-dummy, parallel, multicenter comparison.
- After a 4-week, placebo run-in phase, women were randomized 1:1 to CombiPatch and placebo tablets or Prempro and placebo patches for 20 weeks (one patch twice weekly applied on the lower abdomen and one tablet taken daily).
- CombiPatch is a transdermal patch combination of 50 µg E₂/140 µg NETA.
- Prempro is a combined oral tablet containing 0.625 mg CEE/2.5 mg MPA.

Study Population

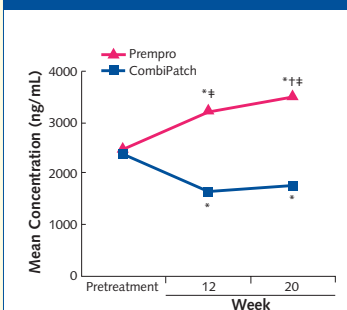
- Healthy women with a uterus who were postmenopausal for 1 to 6 years and have not taken HT within 2 weeks of beginning the 4-week, placebo run-in phase of the study.

RESULTS

Patient Demographics

- Demographic characteristics were similar between treatment groups (Table 1)
- There were no significant pretreatment differences in RS levels between the 2 treatment groups ($P=0.636$) (Table 1)
- RS levels were significantly reduced with CombiPatch from the pretreatment visit to week 12 ($P<0.001$) and week 20 ($P<0.001$), while RS levels significantly increased with Prempro from the pretreatment visit to week 12 and week 20 ($P<0.001$); at week 20, RS levels were also significantly higher than at week 12 with Prempro ($P=0.046$) (Figure 1)
- At weeks 12 and 20, patients on CombiPatch had significantly lower RS levels compared with women receiving Prempro ($P<0.001$) (Figure 1)
- The RS values for all patients were within clinically normal reference ranges.

FIGURE 1. Renin Substrate Levels With CombiPatch and Prempro



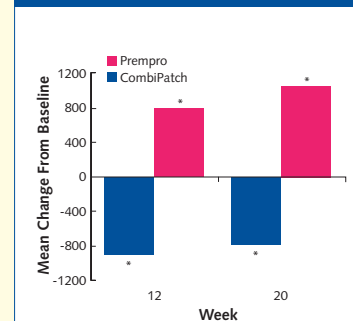
* $P<0.001$ compared to pretreatment visit (4-6 weeks prior to randomization) within treatment group; † $P=0.046$ compared to week 12 within treatment group; ‡ $P<0.001$ between-treatment comparison at the same time point.

- RS levels with CombiPatch were significantly lower than pretreatment values at both weeks 12 and 20 (Figure 2)
- RS levels with Prempro were significantly higher than pretreatment values at both weeks 12 and 20 (Figure 2)

CONCLUSIONS

- RS (angiotensinogen) activates RAAS, which can lead to increased blood pressure.⁴
- Overall, RS levels decreased in patients on CombiPatch and increased in patients on Prempro. RS levels were also significantly higher with Prempro therapy than with CombiPatch.
- These differences, likely due to the differential metabolism of transdermal patch and oral therapies, may make transdermal patch HT more clinically favorable than oral HT.
- Angiotensinogen, an important substrate in the RAAS, is implicated in the development of hypertension; however, this study was not designed or powered to draw any conclusions about the relationship between blood pressure and RS levels.
- Further studies need to be conducted to demonstrate the effects of transdermal patch therapies on hypertension.

FIGURE 2. Mean Change From Baseline in Renin Substrate Levels With CombiPatch and Prempro



* $P<0.001$ compared to pretreatment

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