Transdermal Delivery of Bioidentical Progesterone Using Dutasteride (A 5α-Reductase Inhibitor): A Pilot Study

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ABSTRACT – Purpose. The bioavailability of transdermal progesterone is known to be low and variable. This can be attributed to transdermal metabolism by 5α-reductase enzymes. The objective of the current study is to evaluate the effect of dutasteride, an inhibitor of these metabolizing enzymes, on the bioavailability of transdermally delivered progesterone. **Method.** Twenty postmenopausal women with Follicle Stimulating Hormone levels greater than 40IU/L were recruited to take part in the study. The subjects were randomly allocated to either dutasteride (n=10) or placebo (n=10) groups. Each group applied either 500 mg of non-ionic cream or dutasteride cream (2 mg/g) to the right arm for 15 days. This was followed by applying 500 mg of progesterone (80 mg/g) or progesterone dutasteride cream (80 mg/g, 2 mg/g) for a further two weeks. On day 30, blood and saliva samples were collected over a 12-hour period and progesterone concentrations determined. **Results.** The baseline serum progesterone concentration on day zero was 0.1 ng/ml. On day 30, baseline serum progesterone levels increased significantly ($p < 0.05$) to 1.40 ng/ml and 1.15 ng/ml in the progesterone and dutasteride groups, respectively. Salivary progesterone concentrations were increased by seven fold, from 0.40 ng/ml to 2.9 ng/ml. On average, salivary progesterone concentration was four times the serum levels. **Conclusion.** The average serum and salivary progesterone concentration, C_{max}, and the AUC were slightly higher in the dutasteride group, but no significant difference could be noted. Metabolism by the 5α-reductase enzyme is unlikely to affect the bioavailability of progesterone.

INTRODUCTION

Progesterone is a C-21 steroid hormone involved in mammary gland development, pregnancy, and menstrual cycle. Endogenous progesterone is derived from pregnenolone. Exogenous or bioidentical progesterone is chemically identical to the endogenous form. However, it is synthesized from diosgenin a compound extracted from Mexican wild yam. Bioidentical hormones are popular amongst menopausal women due their limited adverse effect profile (1). Various formulations of progesterone have been developed and investigated, with oral (2), vaginal (3), and intramuscular (4) formulations capable of achieving rapid plasma concentrations matching those usually observed during the luteal phase of the female menstrual cycle (>5 ng/ml). Of the available formulations, only progesterone cream has been investigated for management of menopausal hot flushes (5), osteoporosis prevention (6) and endometrial protection (7). However, the results from most clinical trials are controversial. In one study, transdermal progesterone cream, applied for 14 days in three menstrual cycles, even at relatively high doses (64 mg), did not prevent the proliferative effects of estrogen on the endometrium (8). Conversely, Leonetti et al. demonstrated that transdermal application of 15–30 mg of progesterone daily (for six months) can significantly reduce endometrial proliferation, compared to the placebo, in postmenopausal women treated with 0.625 mg of conjugated equine estrogen (CEE) (9). Additionally, Landes et al. have shown that the endometrial antiproliferative effect of progesterone cream (40 mg/day for six months) was comparable to that of oral medroxyprogesterone acetate (2.5 mg/day) (10).

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Leonetti et al. reported that 83% of the subjects who applied 20 mg/day of progesterone cream for one year showed significant improvement in vasomotor symptoms (1). Conversely, a recent study by Benster and colleagues showed that progesterone cream even at high doses such as 60 mg/day (six months) is no more effective than placebo for the management of vasomotor symptoms (11). However, the duration of this study (six months) was much shorter than the study reported by Leonetti et al. These controversial findings might be due to poor and variable bioavailability of transdermal progesterone.

In a study by Carey et al., 24 postmenopausal women applied progesterone cream for six weeks at either 20 mg twice daily or 40 mg once daily (12). The plasma progesterone levels were measured on days 1 and 42. No considerable differences were observed between the two treatment groups. The average maximum plasma concentration was 0.22 ng/ml on day 1 and increased to 1.6 ng/ml on day 42. In a similar study conducted by Burry et al., six postmenopausal women applied 30–60 mg of progesterone cream for four weeks in combination with 0.05 mg of transdermal estradiol (13). At the end of the study, the average plasma progesterone level increased significantly ($p > 0.05$), from 0.17 ng/ml to 1.6-3.3 ng/ml.

In the studies reported by Carey et al. and Burry et al., a significant increase in plasma progesterone level was noted. However, plasma levels were highly variable and did not surpass 3.3 ng/ml. The circulating level of progesterone during the luteal phase of the menstrual cycle is 4 to 20 ng/ml. Thus, the low plasma progesterone levels observed in these studies may not sufficiently protect the endometrium against estrogenic proliferation or give relief from hot flushes (8). Nonetheless, it has to be considered that plasma progesterone may not reflect the progesterone concentration in other tissues (7). For example, the mean salivary progesterone can rapidly increase to 18 ng/ml within one hour of treatment with transdermal progesterone while the plasma levels remain constant (14, 15). Lee et al. suggests that monitoring the salivary level of progesterone is more important as this value represents the transdermally bioavailable progesterone level (16).

Progesterone is a substrate for the 5α-reductase enzymes present in the skin. It is hypothesized that metabolism by these enzymes may contribute to the low plasma progesterone levels (17). 5α-reductase are membrane-bound steroid enzymes which catalyze the reduction of 4 to 5 double bonds of steroid substrates (18). To date, two genes encoding type I and type II isoenzymes of 5α-reductase have been identified. The former isoenzyme (Type I) is predominately found in the skin and the latter (Type II) is mainly found in the prostate (19). Molecular cloning studies have shown 50% similarities in the amino acid sequence of these isoenzymes (19). Improved bioavailability of transdermally delivered progesterone may be achieved by inhibiting the 5α-reductase enzymes present in the skin. Lewis et al. (14) were the first group to evaluate the effect of enzyme inhibition on the plasma concentration of progesterone. One subject was given 5 mg of oral finasteride, a type II 5α-reductase inhibitor, for nine days followed by 80 mg (40 mg twice a day) of progesterone cream. Although salivary progesterone levels peaked one hour after the first dose of progesterone, no changes in plasma or red cell progesterone concentrations were noted. The authors concluded that metabolism of progesterone is unlikely to affect its plasma concentrations. Finasteride inhibits the type II 5α-reductase enzymes, which have a low distribution in the skin.

To successfully prevent the transdermal metabolism of progesterone, an inhibitor with a strong affinity for the type I isoenzymes is required. Currently, dutasteride is the only FDA-approved non-selective 5α-reductase inhibitor available. Dutasteride has been shown to inhibit the conversion of progesterone to 5α-dihydroprogesterone in tumorigenic breast cell lines (20). Serum and salivary progesterone concentrations may increase by inhibiting the 5α-reductase enzymes present in the skin. The aim of the current study is to investigate the effect of 5α-reductase enzyme inhibition on the serum and salivary concentration of transdermal progesterone.

EXPERIMENTAL METHODS

Study Protocol and Randomization

This study was a randomized, double-blind, single-centre pilot study comparing the effects of topical dutasteride (2 mg/g) on the bioavailability of transdermally delivered bioidentical progesterone. Dutasteride and progesterone cream were extemporaneously compounded in a non-ionic cream base. Ethics approval was obtained from

Tehran University of Medical Sciences (9414). All participants were required to give written, informed consent before the start of the study. Twenty-three menopausal women between the ages of 40 and 65 years were recruited to take part in the study. None had taken any hormones for at least six months, smoked more than five cigarettes per day, or had any skin disease. All women were postmenopausal for at least one year with a Follicle Stimulating Hormone (FSH) greater than 40 IU/L. All women were required to have normal liver and renal function to be eligible for the study. Prior to the study, the women underwent a full medical checkup, which included measurements of serum progesterone, estradiol, testosterone, and cortisol, in addition to the assessment of liver, renal, and thyroid function.

Eligible subjects were randomized to treatment groups using computer-generated numbers (Random Allocation Software, Isfahan, Iran) in opaque, sealed envelopes. Subjects in each group applied 500 mg of either non-ionic cream or dutasteride cream (2 mg/g) to the same area of the right arm for 15 days. This was followed by applying either 500 mg of progesterone cream (80 mg/g) or combined cream (80 mg/g progesterone, 2 mg/g dutasteride) for a further 15 days (Figure 1). The creams were packed in calibrated syringes, each containing 43.8 ± 1.50 mg of progesterone with or without 1.10 ± 0.04 mg of dutasteride. The average surface area of application was 239.60 ± 22.50 cm^2. The participants were instructed not to wash their right arms for at least 2 hours following the application of progesterone. Blood and saliva samples were collected on day 30 at increments of 0, 2, 4, 6, and 12 hours after the final application of the cream. Blood samples were centrifuged at 3,000 rpm, and the serum was separated and stored at -20ºC until analysis by enzyme immunoassay.

Steroids containing a 4–5 double bond in the A ring are a substrate for 5α-reductase enzymes (18). Inhibition of these enzymes could potentially increase the endogenous level of hormones such as testosterone and cortisol. Dutasteride has also been shown to significantly increase the TSH levels (21). Therefore, the effects of dutasteride on serum concentration of other hormones including testosterone, estradiol, cortisol, total triiodothyronine (T3), thyroxin (T4), and Thyroid Stimulating Hormone (TSH) were also monitored during the study. Due to the diurnal variation in concentration of cortisol, baseline samples were always collected at exactly 8 a.m. Compliance was monitored via daily phone calls to the participants.

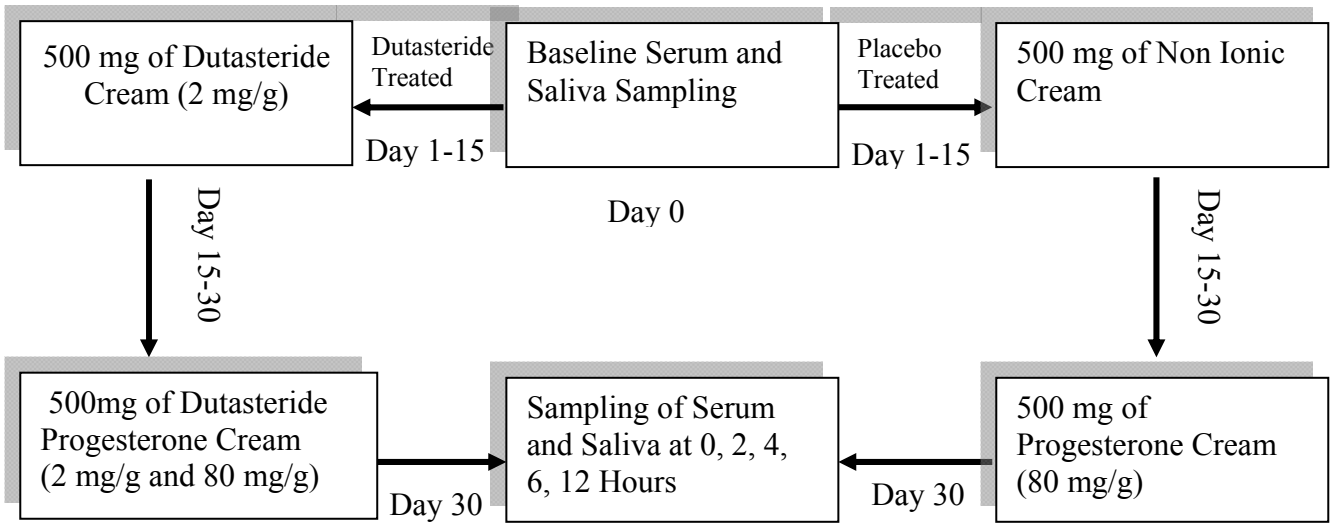

Figure 1: Schematic representation of the study protocol from day 0-30

Sampling of Saliva

A specific protocol was adopted for sampling of saliva. The subjects were instructed not to brush their teeth for at least 12 hours prior to sampling. Samples were taken in accordance with the passive drooling method (22, 23). The head was tilted down, allowing the whole saliva to accumulate in the mouth and dribble into a glass test tube via a glass straw. The samples were collected over the duration of five minutes. The first sample was collected after an overnight fasting; for the other samples, food and drinks were prohibited one hour prior to sampling. The subjects were placed on a strict diet whereby the intake of all dairy products, meat, coffee and juice was forbidden on days 29 and 30 of the study. This was critical because food and drinks may directly or indirectly (via changes in salivary pH and flow rate) interfere with the concentration of drugs in saliva (24). The participants were instructed to rinse their mouths with warm water 30 minutes prior to sampling. After the saliva collection, the samples were stored at -20º C until the time of analysis.

Enzyme-Linked Immunosorbent Assay (ELISA)

Serum progesterone was measured using an IBL progesterone ELISA kit (RE52231, IBL International, Germany). Salivary progesterone was measured using a Demeditec progesterone ELISA kit (DESLV2931, Demeditec Diagnosis, GmbH, Germany). Serum testosterone (EIA-1559), estradiol (EIA-2693), and cortisol (EIA-1887) were measured using DRG ELISA kits (DRG instruments, GmbH, Germany). An EUAgen ELISA kit (Adaltis Italia S.p.A, Casalecchio di Reno, Italy) was used for the measurement of total serum T3 (LI4019B/ LI4026), total T4 (LI4020/ LI4027), and TSH (LI4025K/ LI4028). Serum FSH was measured using an Idealdiag ELISA kit (Idealdiag, Iran).

Assay procedure

Initially 20 to 100 µl of standard, control or sample was dispensed into the appropriate well. To this, 50 to 200 µl of enzyme conjugate was added and mixed for 10 seconds. The samples were incubated at room temperature for 60 to 120 minutes in accordance with the kit's instructions. The wells were then washed 3 to 5 times with the diluted wash solution. After each washing step, the wells were struck against an absorbent paper towel in order to remove any residual water. Following this, 100 to 200 µl of the substrate solution was added to each well, and the samples were incubated for a further 15 to 30 minutes at room temperature. The enzymatic reaction was stopped by adding 100 µl of stop solution. The optical density was then recorded at 450 ±10 nm with a microplate reader (Biochrom Anthos 2010 Microplate Reader, United Kingdom) within 10 minutes.

STATISTICAL ANALYSIS

The following pharmacokinetic parameters were determined and used to study the absorption of progesterone across the skin:

C_{max}: Maximum progesterone concentration achieved in 12 hours
T_{max}: Time to maximum progesterone concentration
AUC_{0-12}: The area under progesterone concentration *v*s. time curve from 0-12 hours calculated using the trapezoidal rule
$C_{average}$: Average progesterone concentration between 0 and 12 hours
$C_{baseline\ 30}$: Baseline progesterone concentration on day 30 prior to applying the last dose of progesterone cream
$C_{baseline}$: Baseline progesterone concentration at the start of the study prior to applying the progesterone cream

All data are reported as median and range. Statistical analysis was performed by the Mann-Whitney U test. $P< 0.05$ was set as the level of significance. The Wilcoxon test was used to compare the baseline hormone levels before and after the application of progesterone or dutasteride cream. All data were analyzed using SPSS software package (SPSS 16.0, USA) and Microsoft Excel 2007 (Microsoft® Office 2007, USA).

RESULTS

Twenty-three postmenopausal women were recruited to take part in the study. Of these women, only 20 were eligible to participate. Ten women were randomized to placebo and ten were randomized to a dutasteride group. Demographics of the study participants are reported in Table 1. No significant differences were observed between the two groups. Two women from the placebo group

and one woman from the dutasteride group withdrew from the study due to non-compliance and loss to follow up. The two-, three-, and six-hour blood samples of three subjects in the dutasteride group and one subject in the placebo group were hemolyzed during sampling and resulted in an abnormally high progesterone concentration (> 50 ng/ml). Hence, the serum results for these subjects were eliminated. Overall serum hormone concentrations were analyzed for six subjects in the dutasteride group and seven subjects in the placebo group. Analysis of saliva data was carried out for all subjects (n=17) that completed the study.

Table 2 summarizes the serum pharmacokinetics data obtained following the application of the progesterone cream for two weeks. The median baseline progesterone concentration on day 0 ($C_{baseline}$) was 0.1 ng/ml in both groups. This is in agreement with the normal range of progesterone reported for menopausal women (25). After 15 days of treatment with progesterone cream the $C_{baseline\ 30}$ increased significantly ($p < 0.05$) to 1.40 ng/ml and 1.15 ng/ml in the placebo and the dutasteride treated groups respectively (Figure 2A). This was followed by a further increase in the serum concentration to a maximum of 5.50 ng/ml (placebo group) and 7.35 ng/ml (dutasteride group) within six to nine hours. By 12 hours, the serum progesterone concentration declined, although it was still significantly higher than the $C_{baseline\ 30}$ level. The average serum concentration of progesterone over 12 hours was 3.04 ng/ml in the placebo-treated group and 3.14 ng/ml in the dutasteride-treated group. Overall, whilst the $C_{average}$, C_{max}, and the AUC were slightly higher in the dutasteride-treated group, no statistically significant difference between the groups was noted.

The salivary pharmacokinetics data are summarized in Table 3 and Figure 2B. On day 30, salivary $C_{baseline\ 30}$ increased sevenfold from 0.4 ng/ml to 2.9 ng/ml in the placebo-treated group with the maximum salivary progesterone concentration observed three to four hours after the last dose of progesterone. The C_{max} and AUC in the placebo-treated group were 21.45 ng/ml and 131.27 ng·hr/ml, respectively. In the dutasteride-treated group, the values had slightly increased to 29.00 ng/ml (C_{max}) and 132.60 ng·hr/ml (AUC), although no statistically significant difference between the groups was noted.

Table 1: The demographics of the study subjects

Demographics	Placebo Treated Group (n=8)	Dutasteride Treated Group (n=9)	p value
Age (years)	53.75 ±4.89	56.88± 3.56	0.25
Body mass index (kg/m^2)	24.31±3.19	26.36±2.70	0.08
Surface area of application site (cm^2)	227.25±22.96	222.50±23.55	0.41
Time since menopause (years)	5.00±2.99	7.07±5.10	0.36
Naturally induced menopause (%)	50	54	0.89
Surgically induced menopause (%)	50	46	0.89

Table 2: Pharmacokinetic parameters of progesterone in serum

Pharmacokinetic Parameters	Placebo Treated Group n=7	Dutasteride Treated Group n=6
C_{max} (ng/ml)	5.50 (2.40-8.10)	7.35 (1.20-25.90)
T_{max} (hr)	6 (2-12)	9 (4-12)
$AUC_{0\text{-}12hr}$ (ng.hr/ml)	34.70 (22.10-58.10)	40.70 (11.2-126.6)
$C_{average}$ (ng/ml)	3.04 (1.78-4.12)	3.14 (0.98-9.80)
$C_{baseline\ 30}$(ng/ml)	1.40 (1-5.4)	1.15 (0.40-3.1)

Data is represented as median (range)

Table 3: Pharmacokinetic parameters of progesterone in saliva

Pharmacokinetic Parameters	Placebo Treated Group n=8	Dutasteride Treated Group n=9
C_{max} (ng/ml)	21.45 (4.80-89.00)	29.99 (3.10-58.00)
T_{max} (hr)	4 (2-12)	3(2-6)
AUC $_{0\text{-}12hr}$ (ng.hr/ml)	131.47 (49.00-398.00)	132.20(20.00-406.00)
$C_{average}$	9.97 (3.88-35.00)	12.17(1.58-37.20)
$C_{baseline\ 30}$ (ng/ml)	2.90 (0.40-7.50)	1.70 (0.46-7.60)

Data is represented as median (range)

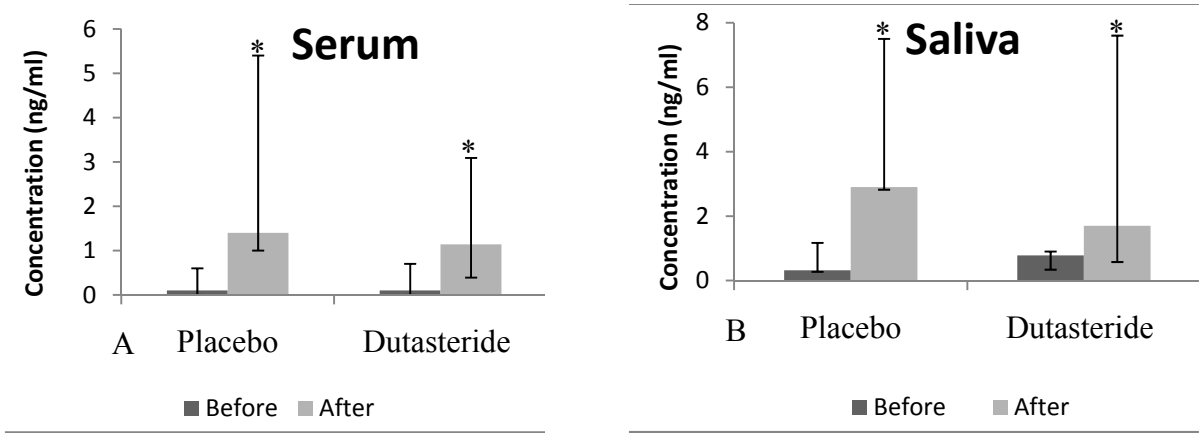

Figure 2: Comparison of baseline serum (A) and salivary (B) progesterone levels before and after application of progesterone in the dutasteride and placebo treated groups. The presented data are median values; error bars represent the range. The asterisk (*) represents a significant increase in concentration ($p<0.05$).

Figure 3 shows the effect of dutasteride cream on the serum level of selected hormones. Of the hormones measured, only TSH showed a significant change following the application of dutasteride cream for one month ($p <0.05$) although its values remained within the normal range. The serum TSH level was increased 1.70-fold, while T3 and T4 levels were slightly reduced. The aforementioned changes were in line with a previous report showing a 1.12-fold increase in the TSH level after 52 weeks of treatment with oral dutasteride (0.5mg/day) (21). The larger increase in the TSH levels seen in this study may be due to the higher dose used or the topical administration, avoiding first-pass hepatic metabolism. This effect is observed for other steroids such as 17β-estradiol, used at 0.5-1 mg/day orally and 0.025-0.10 mg/day transdermally (26). The underlying reason for the increase in the TSH level is not known, although animal studies have established a relationship between thyroid hormones and 5α- reductase expression (27).

Over 30 days, a noticeable increase in the serum estradiol levels was observed in both treatment groups, although the levels were maintained in the normal postmenopausal range (< 65 pg/ml). This increase was greater in the placebo group when compared with the dutasteride group, even though this difference was not statistically significant ($p >0.05$). In premenopausal women, estrogen secretion is cyclic, where the levels rise in the mid-follicular to mid-luteal phase of the cycle (~ day 7 to 25). In postmenopausal women, estrone is the predominant hormone in the serum. The peripheral conversion of estrone to estradiol may contribute to the serum level of estrogen observed in this study (28).

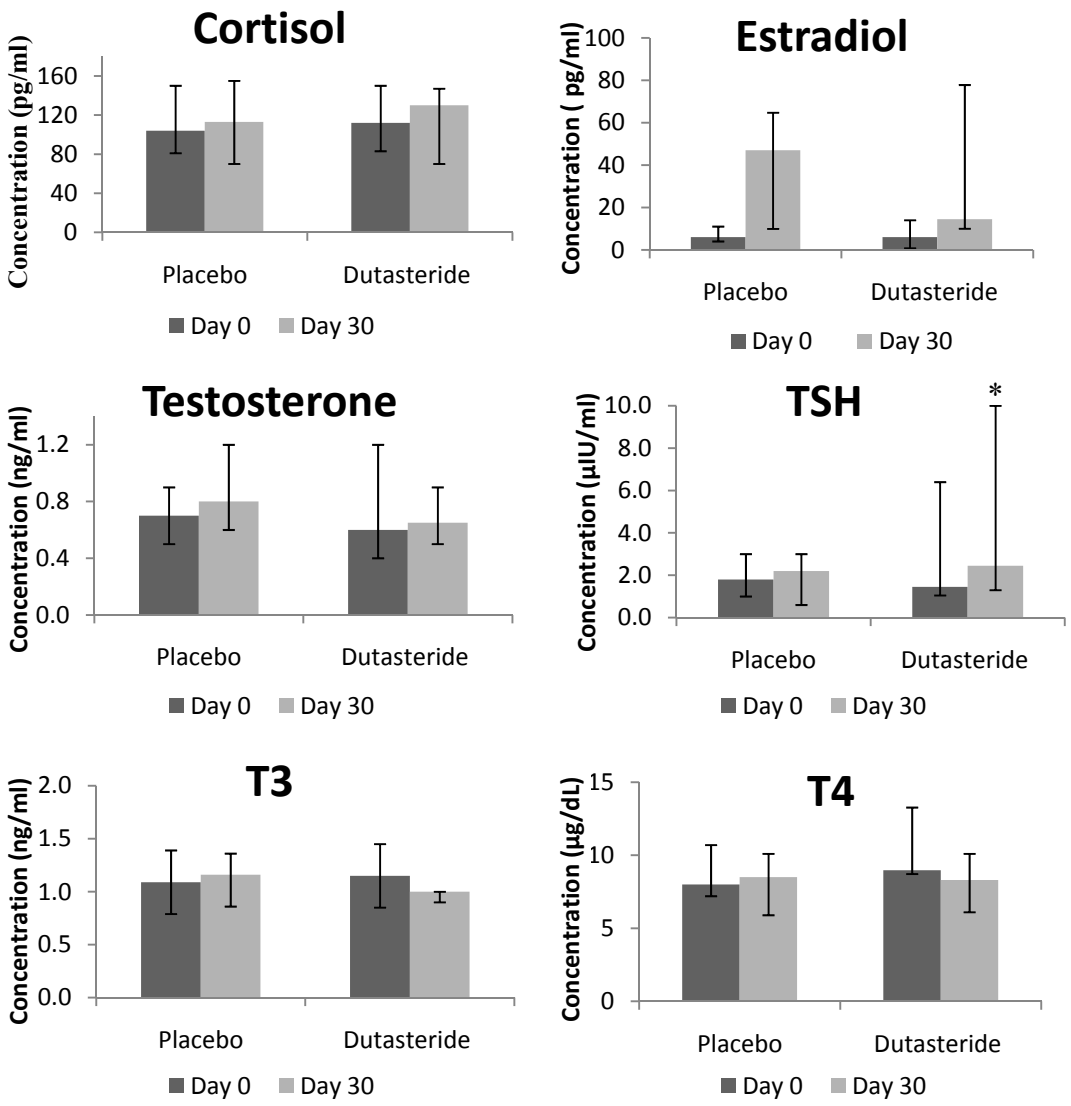

Figure 3: Comparison of the effect of dutasteride and placebo on the serum level of selected hormones. The data is presented as median plus range. The asterisk (*) represents significant increases in concentration.

DISCUSSION

It is hypothesized that cutaneous metabolism of progesterone may significantly reduce its transdermal bioavailability. Therefore, topical dutasteride was used to study the effect of cutaneous metabolism on the bioavailability of transdermal progesterone. This study shows that topical administration of progesterone is associated with a significant increase in the plasma progesterone level. In the placebo-treated group, 15 days of treatment with topical progesterone resulted in a 14-fold increase (0.1 to 1.4 ng/ml) in baseline progesterone level. In general, the percutaneous absorption of progesterone was low and highly variable, achieving serum $C_{baseline\ 30}$ levels usually associated with the follicular phase of the menstrual cycle. During this phase, plasma progesterone concentration does not surpass 1.4 ng/ml. Conversely, in the luteal phase the levels sharply increase, ranging from 4 to 25 ng/ml. It is widely accepted that luteal progesterone levels must be

attained to achieve maximum therapeutic benefits (29). Wren et al. also found that applying 64 mg/day of progesterone does not increase the plasma concentrations beyond the levels observed during the follicular phase (8, 30). O'Leary et al. suggests that higher doses (>64 mg/day) of transdermal progesterone cream should be used in order to obtain higher plasma levels (31). Nonetheless, luteal plasma levels were not obtained even when progesterone was applied at a dose of 80 mg/day, two to four times its recommended dose (32). Age, hydration and skin condition are among the many factors that affect absorption of drugs across the skin, leading to a large inter-individual variability. It has been reported that the penetration of drug molecules across the skin can vary by up to 45% amongst subjects (33).

This study further showed that dutasteride was not able to increase the bioavailability of transdermally administered progesterone. Although serum and salivary C_{max} and AUC of progesterone were slightly higher in the dutasteride treated group ($p > 0.05$), the overall $C_{average}$ was similar to the placebo treated group (Table 2). Frost et al. studied the extent of progesterone metabolism in various tissues within the body including the vaginal mucosa, neonatal foreskin, and abdominal skin. The number and percentage of metabolites formed were different at various tissues. Relatively less 5α-redcuced metabolites were formed in the abdominal skin (27%) compared to the foreskin (53%) and vaginal mucosa (63%). It was suggested that three other enzymatic pathways might contribute to the metabolism of progesterone in the skin. These enzymes include 20α-ol-dehydrogenase, 3α-ol- and 3β-ol-dehydrogenases. In another study, a significant amount of urinary allopregnanediol, the primary 5α-reduced metabolite of progesterone, was reported following the percutaneous administration of progesterone (34), although other 5α-pregnan derivatives previously reported by Frost et al. were not detected. Therefore, it appears that the metabolism of progesterone across the skin is a complex process involving possibly multiple enzymatic pathways. Moreover, the rate and the extent of 5α-reductase metabolism across the skin is variable and depends on the site of application. The current data suggest that peripheral metabolism by the 5α-reductase enzymes is unlikely to significantly affect salivary or serum concentrations of progesterone. Dutasteride slightly enhanced the serum and salivary C_{max}, although this was not sufficient to achieve $C_{baseline\ 30}$ and $C_{average}$ observed during the luteal phase of the menstrual cycle.

A low serum progesterone level can originate from short time of exposure in the systemic circulation and rapid distribution into the saliva. From the saliva, progesterone can enter the gastrointestinal tract and distribute back to the systemic circulation. Extensive metabolism could take place during such transport process. In the current study, the salivary $C_{baseline\ 30}$ was 30 times the levels of progesterone in menopausal women. The salivary $C_{baseline\ 30}$ increased to 2.90 ng/ml, which was twice the corresponding value in the serum (1.40 ng/ml). In premenopausal women, salivary progesterone levels have shown to correlate well with total and free serum progesterone levels, with both levels increasing during the second half of the menstrual cycle (35, 36). Generally, the unconjugated salivary progesterone concentration reflects the free hormone in the serum, which is 2-10% of the total serum level. The transport of progesterone to the saliva is via passive diffusion and is concentration gradient driven (37). In the present investigation, maximum salivary progesterone concentrations were four times higher than the total serum levels. The median C_{max} was 21.45 ng/ml in the saliva as opposed to 5.50 ng/ml in the serum. Furthermore, no correlation was observed between serum and salivary concentrations of progesterone. Progesterone cannot move against its concentration gradient unless an active transport process is involved. Nevertheless, no such transporters have been reported (38). The mechanism for transport of progesterone to the saliva is debatable and not fully understood. Lee et al. have proposed that the transport of progesterone from the blood to the saliva is via binding to the cytocellular and membrane-associated components of red cells (16). However, Koefoed et al. demonstrated that only 15-30% of the total hormone content present in the whole blood is confined to red blood cells (39). Moreover, Lewis et al. observed a large intersubject variability in the red cell bound progesterone with only a maximum of 0.27 ng/ml binding to the red cell as opposed to 1.1 ng/ml measured in the plasma after eight weeks of treatment with progesterone cream (40mg daily) (14). Hermann et al. were the first to measure the concentration of progesterone in whole blood following the application of the

transdermal cream for 12 days (40). At steady state, maximum whole blood level was less than 1 ng/ml. Therefore, the level of progesterone bound to the red blood cell is too low to account for high levels of salivary progesterone observed in the current study. Further studies are required to investigate the mechanism for transport of progesterone to the saliva. Due to the high variability in salivary progesterone levels and the lack of correlation with serum levels, it has been suggested that salivary progesterone levels cannot be used for monitoring hormone therapy (41-43).

It is hypothesized that the metabolism in the saliva may further contribute to its low plasma levels. The saliva is a mixture of leucocytes, microorganisms, exfoliated epithelial cells and gingival fluid (44). These components may play a significant role in the metabolism of steroids in the saliva. Elattar has found that progesterone is metabolized to 5α and 5β metabolites in patients with inflamed gingival (45). Conversely, the rate of progesterone metabolism in healthy human saliva is low. In effect, the rate of progesterone metabolism is about 9.3 pmol/ml/hr in young subjects and decreases to 6.3 pmol/ml/hr in menopausal women (44). Thus, the metabolism of progesterone in saliva is also unlikely to influence its plasma concentration.

CONCLUSION

Transdermal delivery of progesterone was capable of reaching serum levels ($C_{baseline\ 30}$) usually observed during the follicular phase of the menstrual cycle. However, previous studies have shown that such levels are not adequate to induce secretory changes on proliferative endometrium. No long-term studies have been conducted to compare the effect of transdermal progesterone cream on vasomotor symptoms with its plasma and salivary concentrations. The present study suggests that transdermal metabolism of progesterone by 5α-reductase is unlikely to influence its serum or salivary concentrations. Low plasma progesterone levels may be attributed to the rapid distribution of progesterone to the saliva, although no correlation was found between the serum and salivary progesterone levels. Overall, the transdermal absorption of progesterone across the skin is low and highly variable. While some progesterone was successfully delivered transdermally, in order to achieve higher serum levels, further studies are required to gain a better insight into the mechanism of progesterone delivery across the skin.

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