Percutaneous Progesterone Delivery Via Cream Or Gel Application In Postmenopausal Women –

A Randomized, Crossover Study Of Progesterone Levels In Serum, Whole Blood, Saliva, And Capillary Blood

Running title: Progesterone cream/gel: saliva/blood levels

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Sources of financial support: None

Conflicts of interest/Financial disclosures: None
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ABSTRACT

Objective

We investigated the distribution of progesterone in venous whole blood, venous serum, fingertip capillary blood, and saliva following topical application of progesterone in both cream and gel formulations.

Methods

Ten postmenopausal women were randomized to receive 80 mg of progesterone cream or gel applied daily for 14 days, crossing over after a 14-day wash-out. On the last day of each treatment period venous blood, fingertip capillary blood, and saliva were sampled frequently during the 24 h after the final application.

Results

After progesterone cream or gel application, no increase in serum levels was seen until 2 and 3 h later, respectively, and peak levels were achieved much later (at 8-9 h); the AUC_{0-24h} was significantly higher with cream \((12.39 \text{ ng} \cdot \text{h} \cdot \text{mL}^{-1} \text{ vs. } 8.32 \text{ ng} \cdot \text{h} \cdot \text{mL}^{-1}; \ p=0.0391)\). Whole venous blood levels followed a similar pattern to serum, but were considerably lower. Saliva progesterone showed a peak at 2 h and 6 h after application, and C_{max} was comparable with cream and gel. Saliva AUC_{1-24h} was substantially higher than the corresponding AUC for saliva or whole blood, but did not differ significantly by delivery method \((39.02 \text{ ng} \cdot \text{h} \cdot \text{mL}^{-1} \text{ and } 58.37 \text{ ng} \cdot \text{h} \cdot \text{mL}^{-1}, p=0.69)\). In capillary blood, C_{max} was reached at the same time (8 h) and was similar with both formulations; the AUC_{3-24h} was also similar with both formulations \((1056 \text{ ng} \cdot \text{h} \cdot \text{mL}^{-1} \text{ for cream and } 999 \text{ ng} \cdot \text{h} \cdot \text{mL}^{-1} \text{ for gel})\) but was dramatically higher than the corresponding AUCs for venous serum and whole blood.
Conclusions

After application of topical progesterone, saliva and capillary blood levels were approximately 10-fold and 100-fold greater, respectively, than those seen in serum or whole blood. High capillary blood and saliva levels indicate a high level of absorption and transport of progesterone to tissues. Reliance on serum levels of progesterone to monitor topical dosage could lead to underestimation of tissue levels and consequent overdosage.

Key words: Progesterone, Serum, Saliva, Blood, Cream, Gel
INTRODUCTION

Progestogens are commonly prescribed for postmenopausal women who use estrogen therapy to alleviate menopausal symptoms such as hot flashes and vaginal dryness, as well as to preserve bone health. The progestogen component of such treatment is required in women with an intact uterus in order to prevent estrogen-induced endometrial hyperplasia and endometrial cancer (1). Synthetic progestogens have adverse side effects, e.g., reversal of the beneficial effects of estrogen on serum lipids, weight gain, bleeding and mood changes, and are associated with increased risk of breast cancer (2,3). For this reason, many women are turning to the natural progestogen, progesterone, to treat menopausal symptoms. Oral, transvaginal, and nasal administration of progesterone have been shown to be effective and well tolerated (4-7). However, controversy exists as to the effectiveness of progesterone applied as a cream or gel to the skin, even though the lipid solubility of progesterone predisposes it toward a percutaneous method of administration (8).

The effectiveness of topically administered progesterone cream on endometrial protection has been questioned because sufficiently elevated serum levels of progesterone are not achieved, even at relatively high progesterone doses. It is a widely held assumption that serum progesterone levels >5 ng/mL are needed to inhibit estrogen-stimulated endometrial cell proliferation. Several studies have shown that topical administration of progesterone at physiological to supraphysiological doses ranging from 16-80 mg per day for a duration of 1.4–6 weeks do not increase serum progesterone levels above 3.5 ng/mL (9-14).

Antiproliferative effects on the endometrium have been demonstrated with topical progesterone by some (15), but not others (12,13). Leonetti and coworkers randomized 32 postmenopausal women to receive an oral 0.625 mg dose of conjugated equine estrogens (CEE) plus twice daily dosing of 15 mg, 40 mg, or placebo progesterone cream for 28 days, and showed an antiproliferative effect on the endometrium, even though serum progesterone levels were low (15). A similar anti-proliferative effect
on the endometrium was observed with nasal administration of progesterone. Cicinelli and coworkers (16) randomized 10 postmenopausal women to receive 1.25 mg/day oral CEE for 3-4 weeks plus 34 mg/day progesterone given by nasal spray for the last 5-7 days, or progesterone alone for 6 days; endometrial samples showed secretory changes in the endometrium after progesterone treatment in the women pretreated with estrogens, whereas samples taken just prior to the progesterone treatment showed proliferative changes.

Surprisingly, despite the low serum progesterone levels achieved with the progesterone creams, salivary progesterone levels are very high, suggesting that progesterone levels in serum may not reflect those in tissues (13,14,17). Also, unpublished results from one of the authors’ laboratory (DTZ) have demonstrated that capillary blood, derived from the finger tip, contains much higher levels of progesterone than venous blood (serum or whole blood) following topical progesterone delivery, again supporting the notion that venous blood may underestimate delivery of progesterone to tissues. In addition, in one study (18) investigating the effectiveness of topical progesterone on the breast it was shown that progesterone accumulates to high levels in the breast tissue and inhibits breast cell proliferation stimulated by estradiol, but does not significantly raise the level of serum progesterone beyond the placebo-treated group. The physiological mechanism whereby salivary, capillary blood, and tissue (e.g., breast) (18,19) levels of progesterone rise dramatically to luteal levels and higher with physiological topical progesterone dosing, while venous serum levels change very little, remains unsolved.

If indeed topically administered progesterone is delivering higher levels of progesterone to tissues than is apparent from venous serum testing of progesterone, this could potentially lead to excessive dosing in a futile attempt to achieve physiological serum progesterone levels (>5 ng/mL). To investigate this paradox in more detail we designed a study to compare progesterone levels at various time points in venous serum, venous whole blood, capillary whole blood, and saliva, following topical delivery of progesterone to a group of healthy women. Our goal in this study was to identify a window
period where absorption of progesterone cream or gel is at steady state. Using this data we plan to
determine, in a future study, if using progesterone cream or gel continuously with estrogen can protect
the endometrium. Our secondary goal was to directly compare the absorption rate of progesterone cream
versus gel in a randomized crossover study.

METHODS

A prospective, randomized, crossover clinical trial was conducted from March 2010 to July 2010
at the Clinical Trials Unit (CTU) of the Los Angeles County/University of Southern California Medical
Center. The USC Health Sciences Institutional Review Board approved the study protocol, and all study
subjects submitted written informed consent.

Subjects

Ten postmenopausal women were recruited who were at least 1 year postmenopausal with serum
FSH > 40 mIU/mL and estradiol < 30 pg/mL, and had a normal serum progesterone level, no history of
hormone use within the last month, and an intact uterus. Women were excluded if their body mass index
(BMI) was ≥ 35 kg/m^2, if they had any active heart, lung, liver, kidney, or endocrine disorders or breast or
endometrial cancers, or if they were unable to apply study drug to their inner thigh.

Treatment and Sampling

After consent, eligible subjects were randomly assigned through a computer-generated
randomization scheme to 80 mg of progesterone cream or gel applied daily with nitrile gloves to the inner
thigh for 14 days, with 14 days of wash-out period during which no hormone was applied. They were
subsequently crossed over to the other vehicle for the last 14 days of the study. Metered doses of custom-
compounded progesterone cream or gel were prepared by Rox San Compounding Pharmacy (Beverly
Hills, CA). The cream consisted of 80 mg of progesterone, water, glycerine, stearyl alcohol, cetearyl
alcohol, macadamia oil, vitamin E, panthenol, sodium hydroxide, and citric acid. The gel consisted of 80
mg of progesterone, water, and carbomel. The dose of progesterone in the cream and gel was confirmed by liquid chromatography-mass spectrometry.

On the last day of each 14-day treatment period, study subjects came into the CTU for 24 h of frequent sampling to obtain whole blood, serum, capillary blood, and saliva after applying the designated progesterone cream or gel. Blood and saliva samples were taken just prior to drug application and 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after application of the drug. The blood was processed to obtain whole blood and serum. Whole blood was collected in tubes containing sodium heparin, whereas serum was collected in serum separator tubes. Saliva samples were collected by passive flow into clean, plastic collection tubes after rinsing the mouth with cool water, and were taken at least 45 min apart from any food intake. Capillary blood spot samples were obtained via finger stick using contact-activated lancets (Fisher Scientific) just prior to drug application and at 3, 4, 6, 8, 12, and 24 h posttreatment, and spotted onto specialized filter paper (Ahlstrom grade 226, ID Biological Systems). The papers were air dried at room temperature for at least 1 h and subsequently stored at -70°C. To ensure that blood spot samples were not contaminated by the applied cream or gel, study subjects were instructed to wear nitrile gloves when applying the cream or gel to the inner thighs. Prior to blood collection from the finger, subjects thoroughly washed their hands and wiped the finger with an alcohol swab.

Study subjects recorded any adverse reactions or postmenopausal bleeding in a study diary.

Assays

Progesterone was measured in serum and whole blood by radioimmunoassay (RIA) at the laboratory of one of the authors (FZS) as described previously (20), with the exception that a chromatographic step was added prior to the RIA. Separate 0.5 mL aliquots of serum or whole blood were taken for each assay, and approximately 800 d.p.m. of $^3$H-progesterone, with a high specific activity, was added to each aliquot to follow procedural losses. The steroids were extracted with ethyl acetate:hexane (3:2) to remove conjugated steroids, and Celite column partition chromatography, with
ethylene glycol as stationary phase, was used to eliminate potential interfering unconjugated progesterone metabolites. Progesterone was eluted off the column with isoctane, and after evaporating the solvent, the residue was dissolved in assay buffer, which was then aliquoted to determine procedural losses and for RIA. The sensitivity of the progesterone RIA is 20 pg/mL and the interassay coefficient of variation, on average, ranged from 9-13%.

Progesterone was assayed in dried capillary blood spots by a modification of a method previously described (21). Progesterone standard was prepared by mixing the highest progesterone standard from an enzyme immunoassay (EIA) kit (DRG International, Inc. USA) 1:1 with washed human red blood cells (Red Cross, Pacific Northwest Regional Blood Services, Portland, OR). For blood spot controls, commercial control serum levels 1, 2 and 3 from Bio Rad Laboratories (Anaheim, CA) were mixed 1:1 with washed red blood cells. Seventy-five microliters of prepared standard and controls were spotted onto the filter paper, dried overnight at room temperature and stored in zip-lock plastic bags with desiccant packets at -70°C. Six 6.0 mm blood spot disks from each of the high standard, controls, and subject blood spot samples were punched into deep 96-well plates using an automated blood spot puncher (Wallac MultiPuncher, Perkin Elmer, Wellesley, MA). Five hundred microliters of methanol was added to each well and the plates were sonicated for 3 minutes and incubated on a microplate shaker for 1 h at 37°C to extract steroids. The methanol was then transferred to another deep 96-well plate. This step was repeated with another 300 µL of methanol, which was subsequently added to the same deep 96-well plate and dried under nitrogen. Dried extract was reconstituted by adding 600 µL of T-buffer (phosphate-buffered saline containing 0.1% T904 detergent and 0.05% Proclin antimicrobial) followed by sonication for 3 minutes and shaking for 1 min. A progesterone standard curve was created by serially diluting the extracted high standard with T-buffer. One hundred microliters of extracted standards, controls and samples were used to quantify progesterone following a modified immunoassay procedure using progesterone EIA kits from DRG International. The final absorbance was read at 450 nm using the Wallac Victor2 1420 Multilabel Counter (Perkin Elmer Wellesley, MA). Sensitivity of the dried blood
spot assay is 0.1 ng/mL. The intraassay and interassay coefficients of variation range from 9.1-19.2% at 0.7-28.2 ng/mL. Established progesterone reference ranges for capillary dried blood are ≤ 0.8 ng/ml (postmenopausal and premenopausal follicular phase) and 3.3- 22.5 ng/ml (premenopausal luteal phase).

Progesterone was measured in saliva by a previously described method (22). Following collection, all samples were stored at -70°C prior to analysis. Samples were thawed and particulate matter removed by centrifugation. Five hundred microliters of each sample was transferred to a 96-well polypropylene block along with 50 µL of PBS buffer. Saliva was then transferred from each block onto assay plates for progesterone (DRG Salivary Progesterone EIA). Each 96-well block of samples included 2 blanks and 11 other control samples. One hundred microliters of sample and conjugate were incubated at room temperature for 1 h before washing four times with 300 µL of wash buffer; 200 µL of substrate was then added followed by 0.1M sulfuric acid 30 minutes later. The plates were then read on a spectrophotometer at 450 nm and progesterone levels calculated from the standard curve generated using known standards in the same assay. Sensitivity of the saliva assay is 5 pg/mL. The intraassay and interassay coefficients of variation range from 7-10% at 24-1867 pg/mL.

Statistical analysis

The maximum concentration (C_{max}), time at which it occurred (T_{max}) and area under the curve (AUC) of serial measurements of progesterone over time in serum, whole blood, saliva and capillary blood were calculated for each subject while using cream and gel. The AUCs were calculated with the trapezoidal formula, using either interpolation or substitution of the measurement closest in time when missing values occurred. These pharmacokinetic parameters were summarized as median, 25th and 75th percentiles for each medium and each application method. Within-subject paired comparisons between cream and gel were made with the Wilcoxon signed rank test. Statistical tests were 2-sided at a 0.05 level of significance.

RESULTS
Of the 10 women who completed informed consent, 8 completed the entire study. One of the 8 women only had whole blood and serum collected by venipuncture. Two women completed only half the study due to inability to complete another 24-h sample collection. The final participants were ages 51-61 years (median, 58.5 years) and their BMIs were 20-30 kg/m² (median, 24.5 kg/m²). Results for saliva and capillary blood from 2 women after cream application were excluded because the 0 h sampling time (just prior to progesterone application) showed extremely high progesterone levels; these were attributed to sample contamination during collection, because such high levels were not observed in any of the women at the 24 h sampling time, when no further cream was being applied.

Median progesterone levels in serum (venipuncture), whole blood (venipuncture), saliva and capillary blood (finger stick) over the 24-h sampling period after progesterone cream and gel application are depicted in figures 1-4, and the corresponding pharmacokinetic values of progesterone are shown in Table 1. Large intersubject variability was observed in the progesterone levels and pharmacokinetic parameters for both cream and gel, as evident by the interquartile ranges shown for the pharmacokinetic parameters.

Baseline serum progesterone levels in the 8 study subjects ranged from 0.039 ng/mL to 0.092 ng/mL (median 0.059 ng/mL). Following progesterone cream or gel application, there was no increase in serum progesterone levels until 2 and 3 h later, respectively. Subsequently, the levels remained within a range of 0.4-0.55 ng/mL and 0.3-0.5 ng/mL, respectively, with fluctuations that were more pronounced with gel. C_{max} was a little higher, but was attained at a slightly later time, with cream compared to gel (0.71 ng/mL at 9 h vs. 0.59 ng/mL at 8 h, respectively), whereas, the AUC_{0-24h} was significantly higher with cream (12.39 ng·h·mL^{-1} vs. 8.32 ng·h·mL^{-1}; p=0.0391).

Progesterone levels in whole venous blood showed a similar profile to that observed in serum for both cream and gel, but were lower. The levels fluctuated widely for both delivery methods; however, the fluctuations after cream application were more pronounced. C_{max} and AUC_{0-24h} were significantly higher
(p=0.0391 and p=0.0156, respectively) and $T_{\text{max}}$ was one hour longer with cream. In comparison to serum, the values for $C_{\text{max}}$ and $AUC_{0-24h}$ were substantially lower, and $T_{\text{max}}$ was slightly shorter.

In saliva, there was a pronounced peak of progesterone levels after 2 h with cream; the levels then fell dramatically for 2 h and increased for 4 h before decreasing the rest of the time. A similar profile, with progesterone levels a little lower, was observed with gel, except that in the first 2 h post-treatment the levels were considerably lower. The progesterone $C_{\text{max}}$ was a little higher with cream compared to gel (8.71 ng/mL vs. 7.36 ng/mL, respectively), but $T_{\text{max}}$ was very different between the two methods (1 h vs. 6 h, respectively). Thus, $T_{\text{max}}$ was reached very early after cream application, as compared not only to gel but also to the serum and whole blood with both delivery methods. The $AUC_{1-24h}$ was substantially higher with gel, but this difference was not significantly different.

Progesterone levels were very high in capillary blood, with the profile being similar for cream and gel. $C_{\text{max}}$ was reached at the same time (8 h) with both delivery methods but the progesterone $C_{\text{max}}$ was a little higher with cream compared to gel (65.1 ng/mL vs. 58.7 ng/mL, respectively). The $AUC_{3-24h}$ was slightly higher with cream (1056 ng·h·mL$^{-1}$ vs. 999 ng·h·mL$^{-1}$, respectively), and was dramatically higher than the $AUC$s obtained for serum, whole blood and saliva with both delivery methods.

**DISCUSSION**

In this study we investigated the pharmacokinetics of the distribution of progesterone in venous blood, capillary blood, and saliva following topical application of progesterone. Our results show that following treatment of the postmenopausal women with either progesterone cream or gel, venous serum and whole blood progesterone levels were very low in all the subjects. This is consistent with the findings in several studies by other investigators in which postmenopausal women were treated with progesterone cream at doses of 30-80 mg (8,13,14,23). In these studies serum or plasma progesterone levels were maximal at $< 1$ ng/mL. Similarly, we found the progesterone levels were generally well below 1 ng/mL; the median maximum level was only 0.71 ng/mL. Other studies (9) have observed
slightly higher serum progesterone levels, but well below the range considered as luteal (5-25 ng/mL) and able to counter estrogen-stimulated target tissues. The slightly lower serum progesterone levels in our study are likely due to the fact that we used two purification steps that remove progesterone metabolites that interfere with most commercial serum progesterone immunoassays (24). It is well recognized that immunoassays which do not include appropriate purification steps can overestimate the true values.

The serum progesterone levels achieved when the subjects used the gel were slightly lower than those obtained with the cream, which is likely due to differences in absorption kinetics. In a preliminary study that we carried out previously, in which postmenopausal women were treated with a progesterone gel containing 100 mg of progesterone, serum progesterone levels of 5.9 to 8.0 ng/mL were observed at 2 to 3 h after dosing (25). The discrepancy in the findings can most likely be attributed to differences in the progesterone formulations. The formulations were prepared by two different compounding pharmacies, and the notable difference is that in our previous study alcohol was added to the carbomel (gelling substance) used to prepare the progesterone gel, whereas in the present study only water was used with carbomel.

Whole venous blood progesterone levels in subjects after both cream and gel application were substantially lower than the corresponding venous serum progesterone levels; the median AUC\textsubscript{1-24h} values were 7.51 ng\textperiodcentered h\textperiodcentered mL\textsuperscript{-1} and 4.41 ng\textperiodcentered h\textperiodcentered mL\textsuperscript{-1}, respectively, as compared to 12.39 ng\textperiodcentered h\textperiodcentered mL\textsuperscript{-1} and 8.32 ng\textperiodcentered h\textperiodcentered mL\textsuperscript{-1}, respectively. Our findings are consistent with those reported in another study in which whole blood progesterone levels were substantially lower than in plasma during two 3-week periods in postmenopausal women treated with doses of 20 or 40 mg of progesterone cream twice daily (14). This observation would suggest that progesterone carried in the bloodstream is concentrated in the plasma fraction and not the cellular fraction of the blood. Indeed, Lewis and coworkers (14) noted that progesterone was not present in red blood cells prepared from venipuncture serum.

In contrast to the low progesterone levels found in serum and whole blood in both treatment methods, the salivary progesterone levels were high and the capillary blood progesterone levels were even
much higher. The salivary progesterone levels observed in this study are much higher than physiologic saliva levels, which range from about 75-270 pg/mL during the luteal phase of the menstrual cycle and from about 12-50 pg/mL in postmenopausal women (ZRT laboratory reference range data). These results are consistent with those from several other studies which showed that, while serum and plasma levels change very little after topical progesterone application, saliva levels increase dramatically (13,14,17). Salivary levels of progesterone that exceed physiological levels following physiological or supraphysiological topical progesterone dosing have been consistently observed by multiple laboratories, and this has been interpreted to indicate that it is due to the unique physiology of the salivary gland. Indeed, there is more blood flow to the salivary glands than most other tissues, e.g., about 10 times higher than in exercising muscle. Furthermore, there are two capillary beds in salivary glands, one at the level of the salivary duct and the other at the acinar glandular tissue that could result in a higher transport of progesterone into saliva. The very high levels of progesterone in capillary blood are consistent with administration of the supraphysiologic doses (80 mg) of progesterone used in our study. In the laboratory of one of the authors (DTZ), clinical test results of well over 10,000 patients have shown that topical administration of progesterone at physiological doses (10-30 mg) results in a physiological luteal level of capillary progesterone ranging from about 20-30 ng/mL. These results with clinical samples are consistent with the present study where the median progesterone C_{max} values were 65.1 ng/mL and 58.7 ng/mL after 80 mg of cream and gel application, respectively, which are in the order of 100-fold higher than in venous blood.

From a clinical perspective, there would be a very different interpretation of the serum, saliva and capillary blood progesterone data obtained in the present study. The serum results would suggest that progesterone absorbs poorly through the skin when applied in a cream or gel, and that this is not a viable delivery method. In contrast, the salivary and capillary blood results show high levels of progesterone suggesting that serum levels significantly underestimate the delivery of progesterone to tissues.
The much higher levels of progesterone that we observed in capillary whole blood taken from the fingertips compared with serum or venous whole blood, coupled with the high saliva concentrations, raises some questions regarding the mechanisms by which progesterone might be transported through the body following topical administration. Based on the results that progesterone could not be found in red blood cells, Lewis and coworkers (14) suggested the possibility that progesterone may travel to the saliva via the lymphatic system. The lymphatics parallel the vascular system for blood transport, and both systems are present in the capillary beds of tissues such as the salivary glands and the fingertips. In tissue capillary beds, small molecules with molecular weight less than 600, such as steroid hormones, glucose, and oxygen, transfer by passive diffusion between the capillary blood vessels, the interstitial fluid surrounding the target cells, and the lymphatic vessels nearby, and are carried through the lymphatic system to other tissues, such as the salivary glands, endometrium, and breasts. Magness and Ford (26) studied estrogen and progesterone concentrations in uterine lymph and systemic blood during the estrous cycle in pigs, and found that the steroid levels correlated positively in the two fluids throughout the cycle; they note that the small molecular size of the steroids allow them to freely exchange between the two fluids via the intercellular gaps between lymphatic capillaries in the uterus. Blood taken from the fingertip consists of components from the lymphatics, the blood vasculature, and the interstitial fluid bathing these vessels, and is likely representative of fluids present in most other tissues in the body. Our finding of progesterone levels in the capillary blood that are 100-fold those seen in venous blood, and that peak around 8 h after topical progesterone administration, offer support to the hypothesis that progesterone may be transported via the lymphatic system after topical administration. It is equally plausible that progesterone weakly binds to red blood cells as it enters the arterial circulation and is quickly delivered to the interstitial fluid where it can then equilibrate with target tissues, the blood vasculature and lymphatics.

Whatever the mechanism of transport, we suggest that progesterone absorption is much more efficient than has been reported based solely on venous serum or plasma levels measured after topical application. Our findings that salivary and capillary blood levels of progesterone increase dramatically, in
addition to published observations of direct therapeutic effects of progesterone on the endometrium with topical progesterone application, confirm the distribution of progesterone to tissues despite low serum levels. While the mechanism of progesterone absorption, entry into the blood vasculature or lymphatics, and delivery to tissues remains unclear, we can conclude that the use of conventional venipuncture serum or plasma results in a gross underestimation of tissue exposure and clinical efficacy of topical progesterone. We believe that topical progesterone is well absorbed and should be reconsidered as an effective means of treating clinical conditions that respond favorably to progestogens.

ACKNOWLEDGEMENTS

The authors wish to thank Mark Newman, M.S. for carrying out the saliva testing, Sonia Kapur, Ph.D. for the blood spot analyses, and Margaret Groves, M.Phil., E.L.S. for her help with preparation of the manuscript.
REFERENCES


Figure 1. Median progesterone levels in serum for subjects prior to and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after application of 80 mg of progesterone in cream and in gel formulations.

Figure 2. Median progesterone levels in whole blood for subjects prior to and at 1, 2, 3, 4, 6, 8, 12, 16, and 24 h after application of 80 mg of progesterone in cream and in gel formulations.
Figure 3. Median progesterone levels in saliva for subjects prior to and at 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h after application of 80 mg of progesterone in cream and in gel formulations.
Figure 4. Median progesterone levels in capillary blood for subjects prior to and at 3, 4, 6, 8, 12, and 24 h after application of 80 mg of progesterone in cream and in gel formulations.
Table 1. Paired comparisons of cream vs. gel for median pharmacokinetic parameter values of progesterone in serum, whole blood, saliva and capillary blood

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