Over-the-Counter Progesterone Cream Produces Significant Drug Exposure Compared to a Food and Drug Administration–Approved Oral Progesterone Product

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Progesterone products are available in prescription form as well as over-the-counter (OTC) topical preparations sold for "cosmetic" uses. In a randomized study design, the authors compared the drug exposure from an OTC progesterone cream to a Food and Drug Administration–approved oral preparation at the labeled daily doses recommended for each product. Twelve healthy postmenopausal women received 200-mg oral progesterone capsules once daily for 12 days or progesterone cream 40 mg twice daily for 12 days. At steady state (day 12 of each phase), whole-blood samples were collected over 24 hours (oral progesterone) or 12 hours (topical progesterone) and assayed for total progesterone concentration. No significant differences were found in dose-normalized 24-hour progesterone exposure comparing the cream to oral capsules (median $AUC_{0\text{-}24}$ 12.5 ng•h/mL vs 10.5 ng•h/mL, respectively; P = .81). In light of the potential risks associated with long-term progesterone use, the authors question whether topical progesterone products should be available OTC.

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Endogenous progesterone is produced by the adrenal glands, ovaries, placenta, and testes. Progestogens, the term used for a wide range of chemicals that have progestational properties, are most often prescribed as a component of oral contraception or hormone replacement therapy. Progesterones are also administered for treatment of amenorrhea, premature labor, and infertility.[1] The most commonly prescribed progestogens are progestins, which are synthetic compounds such as medroxyprogesterone acetate. Natural progesterone, termed *progesterone USP*, is synthesized from plant sources. In contrast to progestins, progesterone USP is structurally identical to endogenously produced progesterone. A number of Food and Drug Administration (FDA)-approved forms of natural progesterone are available and include micronized oral capsules, vaginal gel, topical progesterone gel, and intramuscular preparations.

Natural progesterone cream (progesterone USP) products can be purchased over the counter (and over the Internet) in the United States as well as other countries. Progesterone cream is categorized as an herbal beauty product and as such is not regulated by the FDA.[2] The cream is advertised as a substitute for other forms of prescription progestogens as well as for treatment of a wide array of syndromes for which there is minimal scientific evidence of efficacy. Symptoms that progesterone cream purportedly treat include premenopausal syndrome, postmenopausal symptoms (eg, fatigue, hot flashes, allergies, breast tenderness, memory loss), osteoporosis, thyroid dysfunction,

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weight gain, autoimmune disorders, irritability, and depression.[3] These claims, in conjunction with marketing progesterone USP as "natural," have led to a widespread popularity of the cream.

Oral micronized progesterone is an FDA-approved product indicated for the prevention of endometrial hyperplasia in women with intact uteruses who receive conjugated estrogens. If the over-the-counter progesterone cream and oral progesterone products provide similar systemic exposure, their therapeutic and safety profiles are expected to be similar. Contradictions exist in the scientific literature regarding whether topical progesterone cream is absorbed in sufficient quantity to prevent endometrial hyperplasia.[4,5] In addition, many pharmacokinetic studies[6-13] comparing topical progesterone to FDA-approved products are inconclusive because of flawed analytical techniques for quantifying systemic progesterone USP absorption.[14] In general, previous studies have used immunoassays that detect both parent drug and metabolites.[4,5,14] In addition, previous studies have examined serum progesterone and not whole-blood progesterone.

If the progesterone in the over-the-counter cream provides significant absorption, women using it may be at risk for adverse effects secondary to progesterone exposure.[15-18]

The specific aim of this study was to compare the exposure of an over-the-counter progesterone cream to an FDA-approved micronized progesterone capsule. The cream used was selected for this study because it is the agent that has previously been studied in the literature.[4,5]

METHODS

The Institutional Review Board of Bassett Healthcare (Cooperstown, New York) approved this study. All subjects provided written informed consent prior to initiation of any study procedures.

Subjects

Subjects were recruited by advertisement within the institution. Healthy women were eligible for the study if they were postmenopausal (defined as being without menses for 6 or more months when associated with appropriate age, hot flashes, or history of bilateral oophorectomy). Women were excluded if they had a history of peanut allergy, breast cancer, endometrial hyperplasia, endometrial cancer with the uterus still present, abnormal uterine bleeding since the last menstrual period, hypertriglyceridemia, thrombophlebitis, severe depression (defined as previous suicide attempt or psychiatric hospitalization), or liver dysfunction (alanine aminotransferase or aspartate transaminase >1.5 times the upper limit of normal). Subjects could not drink more than the equivalent of two 12-oz beers per day, could not be receiving any form of hormone replacement therapy or antiestrogen therapy, and could not be taking any drugs known to inhibit CYP3A activity. Subjects were determined to be healthy by complete medical history and physical examination. Baseline follicle-stimulating hormone (FSH) was used to ensure postmenopausal status.[19] An FSH higher than the peak for menstruating women (except for the midluteal surge) was considered to be within the postmenopausal range. For the assay used, an FSH >20 mIU/mL was considered in the postmenopausal range.

Drug Administration

The trial consisted of 2 randomized, crossover, unblinded phases in which each subject served as her own control. Equal numbers of women were randomly allocated to begin oral or topical progesterone first. There was a minimum 1-month washout period between phases. The daily dosages and instructions for administration of progesterone were based on the package insert recommendations of the respective products. Dosing duration was designed to achieve steady-state concentrations. Dosing did not continue until 21 days as recommended in the topical progesterone package directions since this duration was deemed unnecessary to meet the goals of the study (examination of progesterone exposure at steady state).[4,8]

During the topical drug phase, the women applied progesterone cream (Pro-gest; Transitions for Health Inc, Portland, OR; lot A040328, expiration November 2003) 40 mg twice daily for 12 days, according to the package directions.[2,20] Each 2.5-mL dose of cream was measured out using a calibrated teaspoon and rubbed onto the inner arm, breast, abdomen, or thigh in a site-rotating fashion as recommended by the manufacturer. The area of application was not occluded or washed after cream application. During the oral drug phase, women took micronized progesterone (Prometrium; Solvay Pharmaceuticals, Marietta, Ga; lot 184711, expiration September 2003) 200 mg by mouth daily for 12 days. Women began the first dose of progesterone cream at 8:00 PM and micronized progesterone at 8:00 AM on the first day of each phase so that all final doses were at 8:00 AM on day 12. Women completed both phases as outpatients, with the exception of the final dose of each agent in which they were admitted to the

research unit throughout the first 12 hours of sampling (for oral progesterone, the final sample was obtained as an outpatient).

Sample Collection

Progesterone concentrations in whole blood were assessed at baseline and then serially on day 12 when the drug concentrations were estimated to be at steady state. Whole-blood sampling was done since progesterone is highly lipophilic and has been shown to bind to red cell membranes and albumin.[21] For each preparation, sampling took place over 1 dosing interval at steady state. On day 11 of each phase, women fasted from midnight to 8:00 AM on day 12. Progesterone cream was administered on the inner thigh at 8:00 AM on day 12, and whole-blood samples were obtained via an antecubital or forearm intravenous catheter flushed with 10 U/mL of heparin in 0.9% sodium chloride. Blood samples were obtained at 0, 2, 4, 6, 8, 10, and 12 hours. At 8:00 AM on day 12 of the oral phase, a 200-mg oral progesterone capsule was taken (in the fasted state) with 240 mL of water, and blood samples were collected at 0, 1, 2, 4, 6, 10, 12, and 24 hours. Seven-milliliter blood samples were drawn into heparinized tubes. Whole blood was divided into 2 aliquots and immediately frozen at –80°C until analysis. Following treatments on the blood-sampling days, subjects continued to fast for 4 hours and then resumed a regular diet.

Whole-Blood Progesterone Assay

Progesterone concentrations were determined in whole blood by liquid chromatography-tandem spectrometry (LC-MS-MS), using d9-progesterone as the internal standard and atmospheric pressure chemical ionization. Blood samples were extracted with methyl-t-butyl ether, followed by evaporation of the ether and reconstitution of the extracts with a mixture of methanol and ammonium formate. The reconstituted extracts were injected onto a reversed-phase liquid chromatography column and eluted with a mobile phase consisting of methanol and ammonium acetate. The following MS/MS transitions were monitored:

For progesterone: m/z 315 → m/z 97
For D9-progesterone: m/z 324 → m/z 100

The retention times for progesterone and D9-progesterone were 3.3 and 3.2 minutes. The assay's lower limit of quantitation was 100 pg/mL. The intraday and interday coefficients of variation were 5.2% and 7.6%, respectively.

Data Analysis

Noncompartmental analyses of whole-blood progesterone concentrations were performed. WinNonlin version 3.1 (Pharsight Co, Mountain View, Calif) was used to determine the steady state area under the whole-blood concentration versus time curve from 0 to 12 hours ($AUC_{0\text{-}12}$) for progesterone cream and $AUC_{0\text{-}24}$ for oral progesterone. AUC was used as a measure of exposure. The AUC for the progesterone cream was normalized to an 80-mg/24 h total dose ($AUC_{0\text{-}12}$ was multiplied by 2) to determine the total daily exposure compared to using the once-daily 200-mg dose of oral progesterone. AUC data were log-transformed before statistical analyses. Significance testing was used in this study, with the null hypothesis being no difference in exposure between the 2 products. The 2-sided Wilcoxon rank sum test was applied to log-transformed AUCs using Systat 9.0 (Systat Software Inc, Point Richmond, Calif) to determine whether there was a significant difference in progesterone exposure between the 2 products when used according to package labels. Data are presented as the mean ± standard deviation or the median, as appropriate. A P value of ≤.05 was considered significant.

Sample size was based on the July 2002 FDA Guidance for Industry: Bioavailability and Bioequivalence for Orally Administered Drug Products—General Considerations. This guidance suggests that a sample size of 12 is appropriate for an initial study of either oral or topical preparations.[22] When using significance testing, 12 subjects would have a 75% power to detect a 25% difference in exposure.

RESULTS

Thirteen Caucasian women were enrolled in the study. Twelve women completed the study and are included in this analysis. The mean age for the 12 women completing the study was 54.6 ± 7.0 years, and the mean weight was 77.2 ± 16.6 kg. One subject who received topical progesterone was withdrawn from the study during the washout interval (prior to the oral progesterone phase), and her data are not included in this analysis.

Whole-Blood Progesterone Concentrations

No measurable progesterone concentrations were found in any woman at screening or prior to the start of either progesterone treatment phase, indicating that the women were postmenopausal. Mean whole-blood

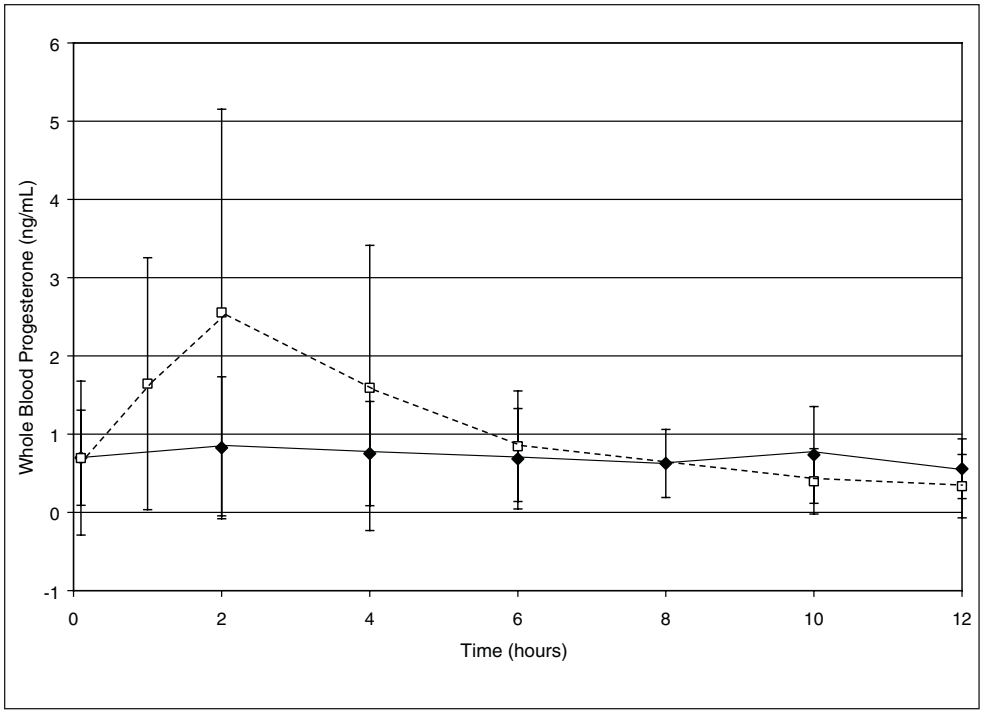

Figure 1. Twelve-hour mean (SD) progesterone whole-blood concentration versus time profiles following an oral (□) 200-mg dose versus a topical (◆) 40-mg dose in 12 women. The mean progesterone serum concentration (SD) at 24 hours for the oral 200-mg dose was 0.14 ± 0.18 ng/mL.

concentrations after administration of topical and oral progesterone at each collection time point with standard deviations are provided in Figure 1. The mean (±SD) steady-state $AUC_{0\text{-}24}$ for 80 mg of topical progesterone is compared to the $AUC_{0\text{-}24}$ for 200 mg oral progesterone in Figure 2. The median $AUC_{0\text{-}12}$ of topical progesterone (normalized to 80 mg/24 h) was 12.5 ng•h/mL (range, 3.8-46.6; 95% confidence interval [CI], 8.3-25.8). The median $AUC_{0\text{-}24}$ of oral progesterone was 10.5 ng•h/mL (range, 2.9-48.2; 95% CI, 8.3-25.7). No significant difference was seen in the 24-hour exposure between the cream and oral capsule ($P = .81$).

Adverse Events

During the oral progesterone phase of the trial, 1 subject developed a headache and another experienced neck pain. A third subject developed a headache while receiving topical progesterone. One subject was diagnosed with intraductal breast carcinoma in situ during the washout interval (following the topical progesterone cream phase) and was removed from the study. This adverse event was deemed not related to progesterone treatment.

DISCUSSION

Our data show that 1 brand of progesterone cream does not produce significantly different steady-state drug exposure (AUC) when compared to an FDA-approved oral progesterone preparation at daily doses recommended by the package inserts.[2,20] The results of this study are more accurate than most previous progesterone pharmacokinetic studies because of sampling of whole blood, more extensive blood sampling, measurement of total progesterone, and use of progesterone-specific assay techniques.

Orally administered progesterone undergoes a large first-pass effect. The drug is metabolized into breakdown products by the liver prior to entering the bloodstream and produces metabolites that cross-react with the immunologic assays commonly used in other progesterone studies.[13,23] Most previous studies reporting oral progesterone exposure data[4,6,7,10-12,24,25] have reported erroneously elevated exposures due to assay cross-reactivity. Our findings are consistent with other studies that employed LC-MS-MS analytical techniques to separate progesterone from its metabolites.[13,14,23] In our study, the mean steady-state peak

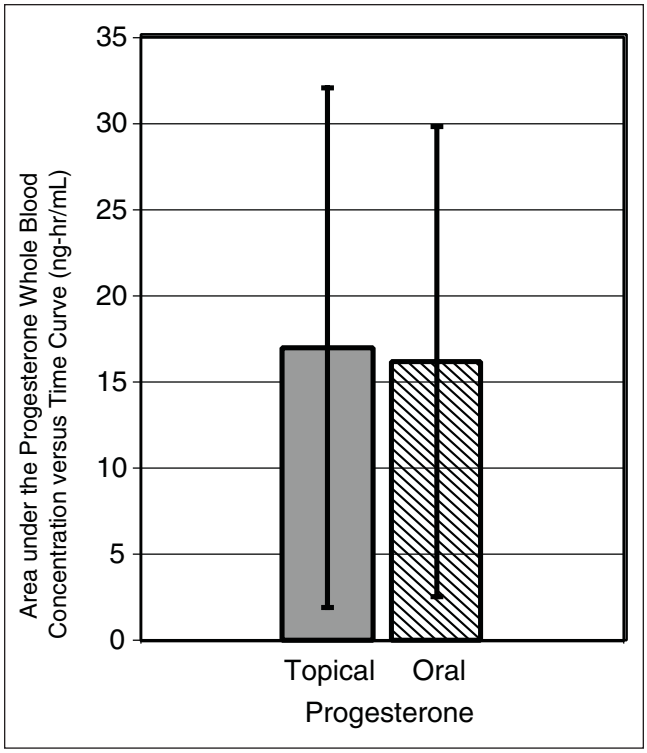

*Figure 2. Comparative 24-hour whole-blood exposure (mean [SD] area under the progesterone serum concentration versus time curve) for oral (200 mg/24 h) versus topical (80 mg/24 h) progesterone in 12 women. No significant difference (*P = *.81) was found for 24-hour exposure between the products.*

whole-blood progesterone concentration (C_{max}) after 200 mg of oral micronized progesterone was 2.8 ng/mL in whole blood. Previous studies using LC-MS-MS report C_{max} ranging from 1.5 to 4.7 ng/mL after 100 to 200 mg of oral micronized progesterone.[13,14,23]

High levels of biologically active metabolites play a role in the activity and side effects of progesterone.[6,26] Data remain unclear on whether similarly high levels of active metabolites are formed from topical progesterone or whether active metabolites are necessary for end-organ response. Because the efficacy of oral micronized progesterone is partially attributable to its metabolites, further studies comparing active metabolites from oral micronized progesterone and topical progesterone are recommended.

Although there are data on the national use of prescription hormone replacement therapy in the United States,[27] we are unable to assess how many women use over-the-counter progesterone creams because the creams can be purchased without a prescription. Our data demonstrate that women who use topical progesterone products are exposed to similar whole-blood concentrations as those who take prescription oral progesterone. However, women are using this medication without medical supervision. Not only are there potential risks of adverse reactions to the progesterone, but there are also risks for drug interactions that may not be identified by the user or her health care provider.[16,28]

Of the large prospective studies of hormone replacement therapy, only the Postmenopausal Estrogen/Progestin Interventions (PEPI) study used micronized progesterone. The other large trials have used medroxyprogesterone, a synthetic progestin that is structurally different from natural progesterone. Although the number of serious adverse events that occurred during PEPI were small, there was no evidence to suggest that natural progesterone is safer than other types of hormone replacement therapy that include synthetic progesterone (medroxyprogesterone).[17,18] In the PEPI study, the small number of breast cancer cases (8 cases) included 4 cases in the estrogen plus micronized progesterone arm.[29] While the breast cancer risk did not differ significantly from that of the synthetic progesterone (2 cases), estrogen alone (1 case), or placebo group (1 case), it may be reasonable to consider natural progesterone at least equivalent to synthetic progesterone (medroxyprogesterone) as a risk factor for development of invasive breast cancer.

The use of topical progesterone without medical supervision is of concern. Since the Women's Health Initiative results were first published in July 2002, prescriptions for progesterone products have fallen dramatically,[27] yet over-the-counter progesterone cream remains accessible to the public. Many women who experience recurrence of vasomotor symptoms after cessation of prescription hormone replacement therapy may turn to over-the-counter products unaware that these nonprescription products yield the same exposure as the prescription oral micronized capsules. Women who use the nonprescription form of this drug do not have the benefits of counseling, screening, and supervision from a health care professional. Given the data suggesting that progesterones can pose a risk, we question whether topical progesterone products should be available over the counter since they give exposure equivalent to a prescription-only product.

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