

# Comparison of the pharmacokinetics of Crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women

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**Objective:** Compare the pharmacokinetics of vaginal progesterone gel (Crinone 8%, 90 mg) with that of oral progesterone (Prometrium, 100 mg).

**Design:** Open-label, randomized, parallel-group protocol.

**Setting:** Outpatient clinic.

**Patient(s):** Twelve healthy postmenopausal women.

**Intervention(s):** Six subjects each were randomized to receive progesterone, which was administered either as 90 mg of progesterone gel (Crinone 8%) given vaginally or 100 mg progesterone in a capsule (Prometrium) given orally.

**Main Outcome Measurement(s):** Serum progesterone levels were measured by both radioimmunoassay (RIA) and liquid chromatography-mass spectrometry (LC-MS).

**Result(s):** Progesterone given vaginally resulted in greater bioavailability with less relative variability in absorption than oral progesterone (mean  $AUC_{0-24} = 1.48 \pm 0.16 \text{ ng} \cdot \text{h/mL}$  per milligram vs.  $0.035 \pm 0.0052 \text{ ng} \cdot \text{h/mL}$  per milligram). Mean  $C_{max}$  for oral progesterone was much lower than that of vaginal progesterone (i.e.,  $2.20 \pm 3.06 \text{ ng/mL}$  vs.  $10.51 \pm 0.46 \text{ ng/mL}$ ). Mean  $T_{max}$  occurred earlier for oral progesterone than for Crinone ( $1.00 \pm 0.41$  hours vs.  $7.67 \pm 3.67$  hours). Radioimmunoassay is inappropriate for determining serum progesterone levels after oral administration, because it provided erroneously high values that were approximately eightfold higher than those obtained with LC-MS.

**Conclusion(s):** Crinone (progesterone gel) given vaginally results in greater bioavailability with less relative variability than oral progesterone, thus providing more reliable delivery of progesterone, compared with oral progesterone. Measuring circulating progesterone with use of direct RIA is not appropriate after oral progesterone administration. (Fertil Steril® 2000;73:516–21. ©2000 by American Society for Reproductive Medicine.)

**Key Words:** Pharmacokinetics, bioavailability, Crinone, vaginal progesterone, micronized progesterone, progesterone gel, progesterone capsule, Prometrium

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Progesterone is currently used to promote fertility, prevent endometrial hyperplasia, and induce withdrawal bleeding. With modifications in dose, duration of treatment, and route of administration, other uses include the induction of amenorrhea, regular bleeding, and atrophic or full secretory changes of the endometrium (1, 2). Thus, the ideal dosage form should produce reliable and predictable delivery and absorption of this natural hormone.

Oral progesterone produces poorly sustained plasma progesterone concentrations (3–5) and is

subjected to considerable first-pass prehepatic (6, 7) and hepatic metabolism (7), leading to its conversion to  $5\alpha$ - or  $5\beta$ -reduced metabolites (6, 8–10). Further reduction at the  $3\alpha$  position yields compounds that bind and allosterically activate the GABA<sub>A</sub> receptor complex, potentially eliciting hypnotic effects (8–10).

Strategies to avoid these problems led to the exploration of clinically acceptable nonoral routes that avoid first-pass liver metabolism of progesterone. Early studies evaluating plasma levels of progesterone after vaginal, rectal, or

intramuscular administration showed that progesterone is readily absorbed, but considerable interindividual variation in plasma levels is seen (11, 12).

Later studies evaluating the effects of vaginally administered progesterone on the endometrium showed that uterine effects exceeded those expected when comparable systemic concentrations were achieved after IM injection (13, 14). Similar findings have been noted after vaginal administration of other drugs such as terbutaline (15) and danazol (16).

These findings led to the hypothesis that a preferential transport of drugs from the vagina to the uterus ("first uterine pass effect") takes place after vaginal administration (17). The vaginal route as an alternative route for systemic administration is particularly advantageous for administration of drugs such as progesterone, which exert their activity on the uterus and are highly metabolized when administered orally.

Recently, a transvaginal Bioadhesive Delivery System consisting of progesterone in a polycarbophil-based gel (Crinone 8%; Serono Laboratories, Norwell, MA) was specifically designed to provide prolonged and controlled release of progesterone after vaginal application. By sustaining the vaginal release of progesterone, this system benefits from the vagina to uterus transport of progesterone and achieves the desired endometrial effects while systemic levels of progesterone remain subphysiologic (18). Furthermore, it produces more stable serum progesterone concentrations over 24 hours (19) and higher endometrial progesterone concentrations than expected during the luteal phase of normal cycles (20), reflecting a strong retention of progesterone at its target organ (1). Thus, this system should produce more sustained and reproducible delivery of progesterone, compared with other systemic routes of delivery.

Furthermore, confusion exists in the literature on circulating levels of progesterone achieved after oral administration of progesterone capsules. For example, Simon et al. (21) report high plasma progesterone levels after oral administration of progesterone, whereas endometrial effects are subphysiological in relation to the circulating levels of progesterone reported. Nahoul et al. (5) provided a putative explanation for this discrepancy by showing much lower circulating progesterone levels when measurements are made after separation on a Celite column.

Hence, we elected to clarify the controversy on circulating progesterone levels after oral ingestion of progesterone capsules and compare the pharmacokinetics of the oral capsule (Prometrium; Solvay Laboratories, Marietta, GA) and vaginal gel (Crinone) after measurement by direct RIA and liquid chromatography-mass spectrometry (LC-MS).

## MATERIALS AND METHODS

### Subjects

Twelve healthy postmenopausal women (50–58 years old) were enrolled in an open-label, randomized, parallel-group study. All subjects provided written informed consent before entering the study. Volunteers were judged to be in good health on the basis of screening data. The protocol was reviewed and approved by the Ethics Review Committee of Inveresk Research International Limited in Edinburgh, Scotland, and conducted according to specifications of the Declaration of Helsinki (1964) and Tokyo (1975), Venice (1983), and Hong Kong (1989) revisions.

Eligible subjects were stabilized on estrogen therapy for at least 3 months before enrollment and had a serum progesterone concentration of not greater than 2 ng/mL at screening. Subjects were excluded from study participation if they had any surgical or medical condition, which, in the investigator's opinion, might interfere with the absorption, distribution, metabolism, or excretion of study drug. Except for estrogen therapy, the consumption of alcohol and other drugs was not permitted before or during the study. Subjects were allowed to use tobacco if they were in the habit of using it.

### Treatment Protocol and Blood Sampling

Within 14 days of study initiation, subjects attended the clinic for screening, which included 12-lead electrocardiogram, vital signs, hematology and clinical chemistry, cervical smear, and testing for hepatitis B antigen, HIV infection, or drug abuse. On the day before the pharmacokinetic study, subjects were admitted to the clinic and fasted overnight for at least 10 hours before dosing and until 3 hours after dosing.

Six subjects each were randomized to receive a single dose of 90 mg progesterone gel given vaginally or 100 mg progesterone in a capsule given orally. Progesterone given orally was administered to each subject with 200 mL of water. A qualified nurse or physician administered progesterone gel to the subject while she was in a reclining position. Time of dosing was recorded for each subject. Subjects remained seated or recumbent for 2 hours after dosing. The resumption of normal activities, excluding strenuous exercise, was allowed 4 hours after dosing.

Venous blood samples (10 mL) for analysis of progesterone were obtained at 0 (predose), 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. The samples were allowed to clot, and the serum was centrifuged for separation and then stored frozen at or below  $-15^{\circ}\text{C}$  until assayed.

Blood was taken for hematology and clinical chemistry at 24, 72, and 96 hours after dosing, and a urinalysis was performed 24 hours after dosing. Before discharge, subjects underwent a brief physical examination and their vital signs were recorded. A gynecological examination was performed at the final visit.

Adverse events were recorded on standardized case record forms, including date of symptoms, their time of appearance, duration and severity, and the investigator's decision regarding its relationship to study drug.

## Assay Methodology

### Liquid Chromatography-Mass Spectrometry (LC-MS) Assay

Progesterone concentrations were measured with use of a validated LC-MS assay that was specific for progesterone (Inveresk Research Institute Report, unpublished). Progesterone was extracted from serum after the addition of water with ethyl acetate. Samples were mixed and separated by centrifugation, and the supernatant was collected. The extract was concentrated, reconstituted in mobile phase (methanol:water, 80:20, vol/vol), vortexed vigorously, and centrifuged. The upper liquid phase was taken for analysis. Samples (20  $\mu$ L) were injected onto a Zorbax RX C<sub>8</sub> column (25 cm  $\times$  4.6 mm) at a flow rate of 1 mL/min. Extracts of serum were analyzed by LC-MS using an ion-spray interface, operating under positive-ion mode. Aldadiene was used as the internal standard. The minimum detectable level of progesterone was 0.1 ng/mL.

### RIA Assay

Progesterone assays were also performed with a standard RIA kit provided by Biogenesis Diagnostic System Laboratories (DSL). The intervariation and intravariation of this assay did not exceed 5.1% and 2.5%, respectively. All samples were run in duplicate, and a mean was determined. Samples with values exceeding that of the highest standard were reassayed after dilution with 154 mM NaCl; those having very low values were reassayed at the discretion of the operator. The minimum detectable level of progesterone was 0.01 ng/mL.

## Statistics

The pharmacokinetic parameters were compared between the two groups with a Student's *t*-test. Because of the small sample sizes, a nonparametric rank sum test (Wilcoxon) was also performed to verify the conclusions. The *F*-test for homogeneity of variances was also performed. Relative variability within each group was assessed with coefficients of variation. A *P*<.05 value was required for rejection of the null hypothesis. All pharmacokinetics parameters have been expressed as the means  $\pm$  SD.

## RESULTS

### Pharmacokinetic Profile of Progesterone

Table 1 presents a summary of the pharmacokinetic parameters evaluated in this study. It is readily apparent that all parameters for progesterone given vaginally are an order of magnitude larger than for progesterone given orally. All parameters were statistically significantly different between

TABLE 1

Pharmacokinetics of progesterone using the LC-MS method after vaginal and oral administration in postmenopausal women.

Parameter	Progesterone gel (90 mg; delivered vaginally) (n = 6)	Progesterone capsule (100 mg; delivered orally) (n = 6)
C <sub>max</sub> (ng/mL)	10.51 $\pm$ 0.46	2.20 $\pm$ 3.06
C <sub>max</sub> (ng/mL/mg) (dose normalized)	0.12 $\pm$ 0.005	0.02 $\pm$ 0.031
C <sub>ave(0-24)</sub> (ng/mL)	5.55 $\pm$ 0.61	0.14 $\pm$ 0.22
T <sub>max</sub> (h)	7.67 $\pm$ 3.67	1.00 $\pm$ 0.41
AUC <sub>0-24</sub> (ng $\cdot$ h/mL)	133.26 $\pm$ 14.61	3.46 $\pm$ 5.15
AUC <sub>0-24</sub> (ng $\cdot$ h/mL per mg) (dose-normalized)	1.48 $\pm$ 0.16	0.035 $\pm$ 0.052

Note: Values are means  $\pm$  SD. AUC<sub>0-24</sub> = area under the drug concentration-time curve from time zero to 24 hours; C<sub>ave(0-24)</sub> = average serum concentration from time zero to 24 hours; C<sub>max</sub> = maximum drug concentration; and T<sub>max</sub> = time to maximum drug concentration. All progesterone gel and progesterone capsule values are significantly different, *P*<.05.

Levine. *Crinone 8% vs. Prometrium*. *Fertil Steril* 2000.

the groups (all *P*<.002 for parametric and nonparametric tests). Thus, peak concentrations of progesterone were much lower and occurred much earlier after oral progesterone (2.20  $\pm$  3.06 ng/mL after 1.00  $\pm$  0.41 hours) compared with vaginal progesterone (10.51  $\pm$  0.46 ng/mL after 7.67  $\pm$  3.67 hours). This, in turn, reflected much greater amounts of progesterone absorbed overall. AUC<sub>0-24</sub> and C<sub>ave(0-24)</sub> for vaginal progesterone were 1.48  $\pm$  0.16 ng  $\cdot$  h/mL per milligram and 5.55  $\pm$  0.61 ng/mL, whereas those for oral progesterone were 0.035  $\pm$  0.052 ng  $\cdot$  h/mL per milligram and 0.14  $\pm$  0.22 ng/mL.

The *F*-test for homogeneity of variances was rejected for all parameters except C<sub>ave</sub>. Although this appears to violate the assumptions for interpreting the tests for differences, it was not considered misleading because of the magnitude of differences observed. The amount of vaginal progesterone absorbed consistently showed less than half the relative variability of oral progesterone. Furthermore, the relative variability for peak concentration levels was about 40-fold less variable for vaginal progesterone compared with oral progesterone.

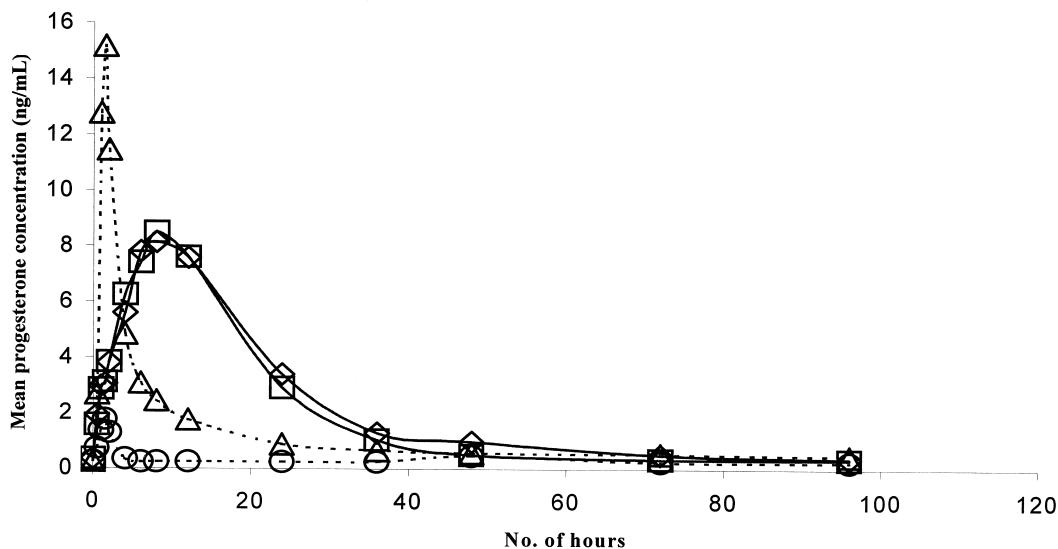
LC-MS data were used to examine serum progesterone concentrations for calculating pharmacokinetic parameters, because RIA was deemed inappropriate for measuring progesterone concentrations after oral administration.

### RIA vs. LC-MS Assay

The serum progesterone concentration vs. time graph for both progesterone formulations, showing the LC-MS and RIA assay results, is presented in Figure 1. The mean peak serum concentration after oral administration of the same

**FIGURE 1**

Mean progesterone concentration (ng/mL) obtained by RIA and liquid chromatography-mass spectrometry.  $\diamond$  Progesterone gel (RIA),  $\square$  progesterone gel (LC-MS),  $\triangle$  progesterone capsule (RIA),  $\oplus$  progesterone capsule (LC-MS).



Levine. Crinone 8% vs. Prometrium. *Fertil Steril* 2000.

dose of progesterone, as measured by LC-MS, was approximately eightfold lower than that measured by RIA (i.e.,  $2.43 \pm 5.01$  ng/mL vs.  $19.40 \pm 12.64$  ng/mL). This discrepancy was attributed to the fact that only chromatographic techniques are useful in separating progesterone from its metabolites, which are produced in much higher amounts after oral administration, but not after vaginal administration. Thus, the supraphysiologic amounts of progesterone metabolites were incorrectly identified as progesterone when RIA was used to measure progesterone after oral progesterone administration, resulting in an overestimation of serum progesterone levels. Hence, the RIA assay was determined to be inappropriate for measuring serum progesterone levels after oral administration. The RIA estimates of serum progesterone concentration after vaginal administration were similar to those measured by the specific LC-MS assay.

## Safety

No changes in vital signs, ECGs, or clinical pathology and no clinically significant laboratory abnormalities were observed for either treatment group during the study. Adverse events experienced by subjects during the study were similar for the two treatment groups.

## DISCUSSION

### Progesterone Administration

Erny et al. (19) and Cornet et al. (20) showed that progesterone given vaginally resulted in greater bioavailability

and more stable plasma concentrations than that achieved with oral administration. The present study also showed significantly more progesterone available over longer periods of time with vaginal progesterone compared with oral progesterone. The relative variability of vaginal progesterone pharmacokinetic parameters was less than half that of oral progesterone parameters and showed almost 40 times less relative variability in peak plasma concentration.

Other investigators have reported high interindividual variability for  $C_{max}$  after administration of oral progesterone (3, 4, 22). Nahoul et al. (22) showed that a progesterone capsule (100 mg) produced a greater mean  $C_{max}$  after vaginal vs. oral administration, but the vaginal route was associated with a fourfold increase in variability ( $4.7 \pm 0.8$  ng/mL vs.  $1.5 \pm 0.2$  ng/mL). These discrepancies might be due to problems inherent in using oral capsule formulations vaginally and/or the limited specificity of the assay techniques used to measure progesterone concentration after oral administration.

The present study confirms this contention because the same sample assayed with use of both RIA and LC-MS techniques produced very different measurements. In any case, because of no gastrointestinal or hepatic first pass metabolism, progesterone given vaginally resulted in greater and more sustained progesterone concentrations, compared with oral progesterone. This finding agrees with that of other investigators (12, 22) and explains why oral progesterone

capsules failed to produce full endometrial secretion, whereas vaginal application produced a secretory endometrium that was indistinguishable from that produced during fully predecidualized cycles (23).

## Progesterone Measurements by RIA vs. LC-MS

Discrepancies between study findings in the mean  $C_{max}$  of progesterone, where progesterone capsules were given at the same or similar doses and by the same route, show that these variances are most likely related to the limited specificity of the assay that was used. In fact, Nahoul et al. (22) previously showed that progesterone metabolites, which are produced in significant amounts after oral administration, may interfere with RIA.

Extensive metabolism of progesterone occurs in the intestine and liver, resulting in the formation of interfering metabolites, especially those that differ from progesterone at the C5 and C20 position (5 $\alpha$ -dihydroprogesterone, 5 $\beta$ -dihydroprogesterone, and 20 $\alpha$ -dihydroprogesterone). Under ordinary circumstances, these metabolites are known to cause minimal cross-reactivity with immunoassay antibodies. However, when present in large quantities, such as is the case after oral administration (i.e., when greater than 90% of the dose is metabolized during first hepatic pass) (5, 22), these metabolites may cross-react significantly. This cross-reactivity appears to be of particular concern when progesterone was measured by RIA either directly (4, 21, 24) or where chromatographic purification was inadequate (3) and led to erroneously high blood levels of progesterone after oral administration.

The present study supports this contention because mean peak serum progesterone concentration after oral administration by RIA was eightfold higher than that measured by progesterone-specific LC-MS (i.e.,  $19.40 \pm 12.64$  ng/mL vs.  $2.43 \pm 5.01$  ng/mL). These results are not likely to be related to any other factor because other conditions that might influence outcome were controlled (i.e., RIA and LC-MS were both used to assay the same serum samples). Figure 1 shows the comparison of progesterone levels measured by both RIA and LC-MS. The present study findings are in agreement with those of Nahoul et al. (5). These authors showed progesterone levels after oral administration of the same dose (100 mg) of progesterone capsules were fivefold lower when adequate assay techniques were used, compared with data reported by Simon et al. (21) who used an inappropriate RIA method.

## Factors That Affect Variability in Progesterone Plasma Levels

Factors that affect the variability in plasma progesterone levels might be related to the differences in absorption rate and bioavailability, which have been related to the vehicle used (21, 25). As described above, a factor that contributes to the poor bioavailability seen after oral administration of

progesterone is the fact that progesterone is extensively metabolized in the intestine and liver (6, 7).

Furthermore, drugs that are administered in aqueous solution are more rapidly and consistently absorbed than those administered in oily solution, suspension, or solid form because absorption occurs almost entirely from aqueous solution (25). Progesterone has poor water solubility; thus absorption depends on availability of water for dissolution. Furthermore, dissolution in oil does not ensure its absorption, because absorption occurs from an aqueous phase. The gel formulation used in the present study provides an aqueous phase for dissolution of progesterone. This differs from nonaqueous formulations that rely on notoriously variable vaginal secretions to provide the aqueous phase for dissolution.

Other factors that can affect absorption and variability of plasma levels include food-drug interactions, age, hormonal status, conditions at the site of absorption (particularly in the gastrointestinal tract), circulation to the site of absorption, and area of the absorbing surface (determined largely by the route of administration) (21, 25). These factors become more important when progesterone is given orally. This agrees with previous reports that have found that progesterone has greater absorption and bioavailability after vaginal administration, compared with oral administration (21, 24). Crinone 8% has been specifically formulated as an oil in water emulsion for vaginal administration, which provides for enhanced (as demonstrated by AUC), reproducible absorption (as evidenced by the small relative variability), and improved bioavailability of progesterone, compared with oral progesterone.

In conclusion, vaginal progesterone gel (Crinone) provides much greater bioavailability and less relative variability than oral progesterone capsules (Prometrium). Furthermore, comparison of serum progesterone levels measured by direct RIA and LC-MS confirms the erroneous nature of values reported using the former method (22). On the contrary, direct RIA is an appropriate method for the measurement of progesterone after vaginal administration.

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