A Randomized, Open-Label, Single and Multidose (Single-Day and Multiple-Day) Pharmacokinetic Study of a Vaginal Micronized Progesterone Tablet (Endometrin®) Compared to Crinone® 8% Vaginal Gel in Healthy Reproductive-Age Female Subjects

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Introduction

A vaginal micronized progesterone tablet (Endometrin®) is currently under development for use in reproductive-age women requiring progesterone support of the endometrium for pregnancy. This study determined the pharmacokinetic (PK) profiles of two dosage regimens (100 mg BID and 100 mg TID) compared to Crinone® 8% vaginal gel in normal, reproductive-age females (Table 1).

Study Design

This single-center, randomized, open-label, PK study included women 18 to 40 years of age with an intact uterus. Eighteen eligible subjects (six per treatment group) were randomly assigned to receive either tablets (100 mg BID or TID) or 8% gel (90 mg QD). The study was divided into four phases: Screening, Single-Day (single day of dosing), Washout, and Multiple-Day (five days of dosing). Blood samples for PK analyses were collected over a 48-hour period during the Single-Day phase and starting on Day 5 of the Multiple-Day phase. A seven-day Washout period separated the Single-Day and Multiple-Day phases of the study.

Table 1.
Subject Demographic Characteristics and Gynecological History

Characteristic	Tablet 100 mg BID (N=6)	Tablet 100 mg TID (N=6)	Gel 90 mg QD (N=6)	Tablet Combined (N=12)	P-value
Race					Across: 0.527[a]
Hispanic	5 (83%)	3 (50%)	5 (83%)	8 (67%)	Tablet combined vs. Gel: 0.615[a]
Caucasian	1 (17%)	3 (50%)	1 (17%)	4 (33%)	
Age (years)					Across: 0.652[b]
Mean (SD)	35.8 (4.96)	32.7 (9.63)	35.5 (2.59)	34.3 (7.48)	Tablet combined vs. Gel: 0.700[b]
Minimum, maximum	29, 40	18, 40	33, 39	18, 40	
BMI (kg/m²)					Across: 0.218[b]
Mean (SD)	24.7 (2.73)	26.0 (1.97)	26.9 (1.17)	25.3 (2.38)	Tablet combined vs. Gel: 0.168[b]
Minimum, maximum	22, 28	23, 28	25, 28	22, 28	
Average Cycle Length					Across: 0.008[c]
Mean (SD)	27.0 (1.55)	29.3 (1.03)	26.5 (1.64)	28.2 (1.75)	Tablet combined vs. Gel: 0.070[c]
Minimum, maximum	25, 28	28, 30	25, 28	25, 30	

SD = standard deviation; BMI = body mass index; Tablet = Endometrin; Gel = 8% Crinone

* Statistically significant difference (p≤0.05).

a p-value from 2-tailed Fisher's exact test.

b p-value from one-way ANOVA or Kruskal-Wallis test, as appropriate.

c p-value from t-test or Wilcoxon Rank Sum test, as appropriate.

Results

In the Single-Day phase, mean C_{max} was 17 ng/mL in the tablet BID group, 19.8 ng/mL in the tablet TID group, and 6.8 ng/mL in the vaginal gel group (Table 2). Figure 1 demonstrates that the progesterone concentrations produced with the vaginal tablet BID approximated steady-state progesterone concentrations 12 hours after the first dose. The TID dosing group reached steady-state concentrations by the end of the first dosing interval of Day 2. However, the gel showed substantial accumulation between Day 1 and Day 5 of treatment, demonstrating that steady-state concentrations had not been achieved within that time (Figure 2).

By Day 5, the mean concentrations were relatively uniform over the entire 24-hour period (Figure 3). Derived pharmacokinetic parameters indicated that the range maintained for Endometrin® TID stayed between a mean C_{max} of 24.1 ng/mL and a mean C_{min} of 10.9 ng/mL, while gel resulted in lower values which ranged between a mean C_{max} of 14.3 ng/mL and a mean C_{min} of 7.4 ng/mL (Table 2).

Figure 3 is a comparative display of the Day 5 serum progesterone concentrations for the three treatment groups. The vaginal tablet regimens provided greater systemic exposures than did the gel QD as measured by the AUC, with values on Day 5 ranging from 264 ng•hr/mL (gel QD), 327 ng•hr/mL (Endometrin® BID), to 436 ng•hr/mL (Endometrin® TID). Both tablet treatments kept concentrations above 10 ng/mL, a progesterone threshold associated with adequate endometrial preparation in the mid-luteal phase, for the entire 24 hours, whereas the gel treatment failed to continuously maintain this level (Figure 3).

Both the vaginal tablets and the vaginal gel were generally safe and well tolerated. All adverse events were mild in intensity. All events resolved without treatment within four days. No deaths, serious adverse events, or adverse events that led to withdrawal of study drug were reported during the study.

Table 2.
Mean Values of PK Parameters

	BID (N=6)	TID (N=6)	Gel QD (N=6)
Day 1 Cmax (ng/mL)	17.0	19.8	6.8
Day 1 Trough (ng/mL)	13.0	9.0	1.1
Day 1 AUC 0-24 (ng•hr/mL)	217	254	60.9
Day 5 Cmax (ng/mL)	16.5	24.1	14.3
Day 5 Cmin (ng/mL)	9.9	10.9	7.4
Day 5 AUC 0-∞ (ng•hr/mL)	327	436	264
Time to steady-state (hr)	12	32	>120
CV	29.9%	23.2%	39.7%

Figure 1.
Single-Day Treatment Phase

Mean (SEM) serum progesterone concentrations for the three treatment groups

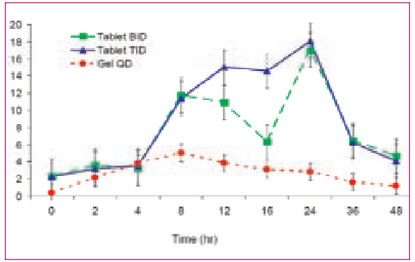


Figure 2.
Mean (SEM) Progesterone Trough Concentrations

During days 1-5 of the Multiple-Day treatment for the three treatment groups

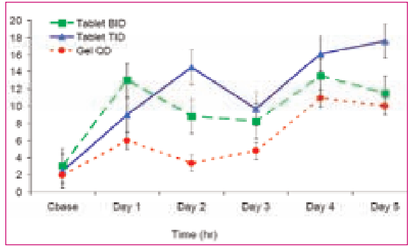
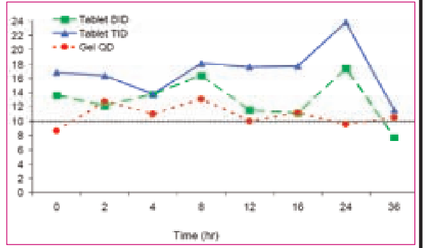


Figure 3.
Day 5 of the Multiple-Day Treatment Phase

Mean serum progesterone concentrations (ng/mL) for the three treatment groups



Discussion

Progesterone serum concentrations increased rapidly following the administration of the Endometrin® vaginal tablet and produced higher peak concentrations in a shorter time than did the vaginal gel. On the single day of dosing, mean C_{max} was 17 ng/mL in the Endometrin® BID group, 19.8 ng/mL in the Endometrin® TID group, and 6.8 ng/mL in the vaginal gel group (Table 2). The tablet treatments also reached steady-state concentrations more rapidly than did the vaginal gel. Steady-state values were attained in approximately 24 hours after initiation of treatment with Endometrin®. The vaginal gel was estimated to require six or more days to reach the steady-state serum concentrations (Figure 2).

Both tablet formulations resulted in concentrations exceeding 10 ng/mL at 12 hours, but vaginal gel required nearly a week to reach this targeted physiological level, nearly half of the two-week post-ovulatory luteal phase which is such a critical stage for implantation. By Day 5, the mean concentrations were relatively uniform over the entire 24-hour period in all three treatment groups (Figure 3). Finally, Endometrin® TID showed the least between-subject variability in C_{max} and AUC, whereas gel QD showed the greatest between-subject variability among the three treatments.

References

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