Single and multidose pharmacokinetic study of a vaginal micronized progesterone insert (Endometrin) compared with vaginal gel in

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Introduction

- IVF / ART -- exogenous luteal phase support
- Endometrial preparation (endo- or exo-genously)
  - Estrogen Endometrial proliferation
  - Progesterone Secretory transformation
    - Available exogenous options: oral, IM, *vaginal formulations*

oral administration

- Convenient
- rapidly cleared by 1st-pass hepatic metabolism low systemic bioavailability requires high doses associated with systemic adverse effects (drowsiness, flushing, and nausea)
- **Pharmacokinetic influenced by food intake**
- **Limited efficacy in inducing an in-**

IM administration

- Rapidly absorbed, 2 hrs -- High plasma concentrations, 8 hrs -- Peak concentrations
- Extremely uncomfortable (oil-based product)
- **Daily** injections maintain adequate [progesterone]s
- Placental autonomy: 10~12 ws protracted use of daily IM injections
- Inflammatory reactions at the injection

Vaginal route

- Avoids the variable absorption, high first-pass hepatic metabolism, uncomfortable (often painful),
- Result in sustained plasma concentrations
- Significant levels of progesterone to the endometrial tissue, inducing secretory transformation

Progesterone

- Available for vaginal administration
- More reliable delivery of progesterone than oral
  - Favorable Pharmacokinetics
  - Greater bio-availability
  - Less variability in serum concentrations
- Equivalent endometrial development and pregnancy rates comparing with IM (cohort observational study)

Endometrin

- A novel vaginal micronized progesterone insert
  - →Luteal support in the Tx of infertile women undergoing ART
- The comparative **pharmacokinetic parameters** of this new vaginal insert and a previously marketed **Vaginal gel progesterone**

Purpose of this study

- Compare Pharmacokinetic & safety profiles
- 2 dosage regimens of the
  - Micronized progesterone 100 mg vaginal insert (twice a day & three times a day)
  - 8% vaginal gel (90 mg every day)
- In Normal, reproductive-aged females with an intact uterus

Principal pharmacokinetic objective

[1] Obtain **single-day** and **steady-state** progesterone pharmacokinetics for the 3 treatment groups

[2] Describe progesterone **steady-state** pharmacokinetics

[3] Compare progesterone pharmacokinetics among the three treatment groups.

MATERIALS AND METHODS

- Guidelines of the University of Miami Human Subjects Research Committee (institutional review board
- Good Clinical Practices and International Council on Harmonization guidelines
- Personnel informed consent before entry into the study
- Phase I Clinical Research Unit of the Division of Clinical Pharmacology of the University of Miami

Study Design

- Single-center, randomized, open-label, parallel design pharmacokinetic study
- Normally cycling female, 18 ~ 40 y/o, intact uterus
- 18 x subjects (6/ Tx group), randomly assigned to receive 1 of 2 different dosing regimens
  - 100 mg vaginal insert (2 or 3 times a day) *(Endometrin, Ferring Pharmaceuticals, Inc., Parsippany, NJ)*

4-Phases

- Screening
- Single-day (Single day of dosing, 24hr)
- Washout (7-day)

– separated the single- & multiple-day

- Multiple day (5 days of dosing)

subjects

- General good health (by medical Hx & PE)
- Regular menstrual cycles (24 ~ 35 days)
- BMI: 18 ~ 28 kg/m2
- Negative Pap smear
- Negative urine pregnancy test
- Randomly assigned to 1 of 3 Tx arms of study medication

- Initiated after menstrual flow ceased
- Between cycle days 5 & 8 of the subject's MC
- ***Single-day phase*** → Drug administered for 1 day
  - Single dose → Every day treatment
  - 2 doses, Q12H → 2 times a day Tx
  - 3 doses, Q8H → 3 times a day Tx
- Blood samples for pharmacokinetic analysis
  - Pre-dose (0 hour)
  - 2, 4, 8, 12, 16, 24, 36, and 48 hours

- ***7-day washout phase***

→ Returned to the phase-I in-patient unit

→ Stay of approximately 6 overnights

→ Received 5 days of treatment during the ***Multiple-day phase***

- On day 5 of medication, Blood samples Pre-dose (0 hour), at 2, 4, 8, 12, 16, 24, 36, and 48 hours after first dosing

Safety parameters

- Adverse events (AEs)
- Serious AEs (SAEs)
- Clinical laboratory evaluations (hematology and serum chemistry)
- Vital signs (blood pressure, heart rate, and body temperature)
- Electrocardiogram

Analytical Methods

- Validated, sensitive, & specific **radio-immunoassay**

- **125-I** labeled progesterone derivative
  →Quantify progesterone concentrations in human serum

- Coefficients of variation for quality control samples

Statistical Methods and Pharmacokinetic Analysis

- Tx group comparisons for demographic and baseline characteristics
- Fisher's exact test qualitative variables and analysis of variance
- Kruskal-Wallis test quantitative variables

Pharmacokinetic parameters

(Single-day & multipledose, multiple-day, Tx day 5)

- Max observed serum concentration (Cmax)
- Time to Max observed serum concentration (Tmax)
- **Area** under the serum concentration (systemic exposure)
  - Time curve over the dosing interval (AUC0–T)

Pharmacokinetic parameters

- Trough (pre-dose) concentrations assess the onset of **steady state**
- **Fluctuation Index** over a 24-hour period :
  - (Cmax-Cmin)/(AUC0–24/24)
  - Cmin was determined by inspection

RESULTS

Subject demographic characteristics and gynecological history.

Characteristic	Insert 100 mg bid (n = 6)	Insert 100 mg tid (n = 6)	Gel 90 mg qd (n = 6)	Insert Combined (n = 12)	P value
Race					
Hispanic	5 (83%)	3 (50%)	5 (83%)	8 (67%)	Across: .627[a] Insert combined versus Ge : .315[a]
Caucasian	1 (17%)	3 (50%)	1 (17%)	4 (33%)	
Age (y)					
Mean (SD)	35.8 (4.96)	32.7 (9.83)	35.5 (2.59)	34.3 (7.46)	Across: .662[a] Insert combined versus Ge : .703[a]
Minimum, maximum	29, 40	18, 40	33, 39	18, 40	
BMI (kg/m^2)					
Mean (SD)	24.7 (2.79)	26.0 (1.97)	25.6 (1.17)	25.3 (2.35)	Across: .219[a] Insert combined versus Ge : .163[a]
Minimum, maximum	22, 28	23, 28	25, 28	22, 28	
No. of pregnancies					
Mean (SD)	2.2 (1.47)	1.3 (1.51)	1.2 (0.75)	1.8 (1.48)	Across: .383[a] Insert combined versus Ge : .383[a]
Minimum, maximum	1, 5	0, 3	0, 2	0, 5	
No. of births					
Mean (SD)	2.2 (1.47)	1.0 (1.26)	0.8 (0.75)	1.5 (1.44)	Across: .145[a] Insert combined versus Ge : .264[a]
Minimum, maximum	1, 5	0, 3	0, 2	0, 5	
No. of abortions					
Mean (SD)	0.0 (0.00)	0.3 (0.52)	0.3 (0.82)	0.2 (0.39)	Across: .605[a] Insert combined versus Ge : .359[a]
Minimum, maximum	0, 0	0, 1	0, 2	0, 1	
Average cycle length					
Mean (SD)	27.0 (1.55)	29.3 (1.03)	26.5 (1.64)	28.2 (1.75)	Across: .003[a] Insert combined versus Ge : .373[a]
Minimum, maximum	25, 28	28, 30	25, 28	25, 30	

Compliance 100%

Pharmacokinetic Results

- Single-day Treatment

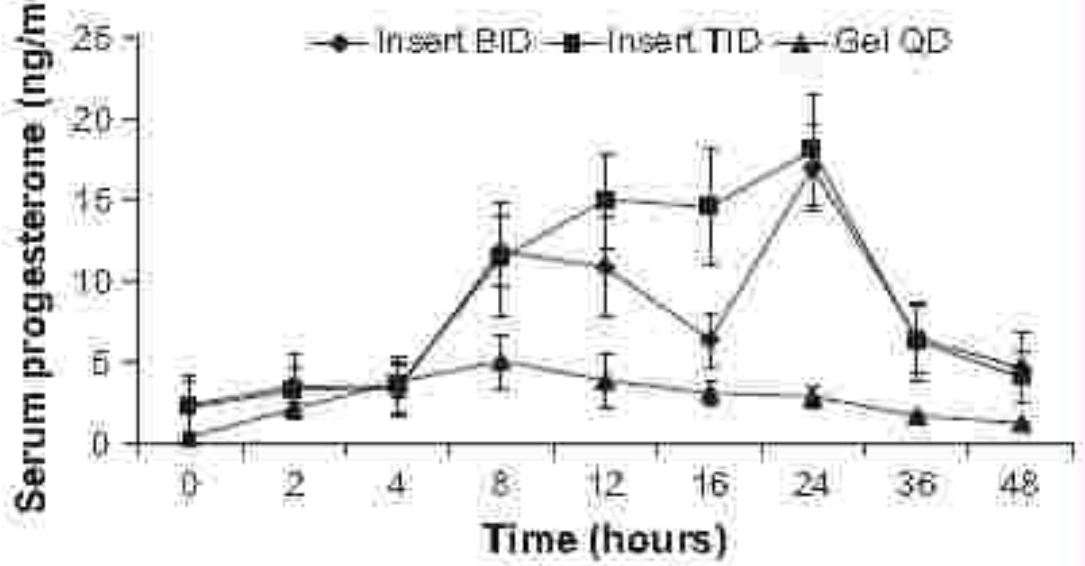
Mean Cmax (ng/mL) / AUC0-24(ng•h/mL):

17/217 (2x/D insert)

19.8/284 (3x/D insert)

FIGURE 1

Single-day treatment phase: mean (±SEM) serum progesterone concentrations (ng/mL).

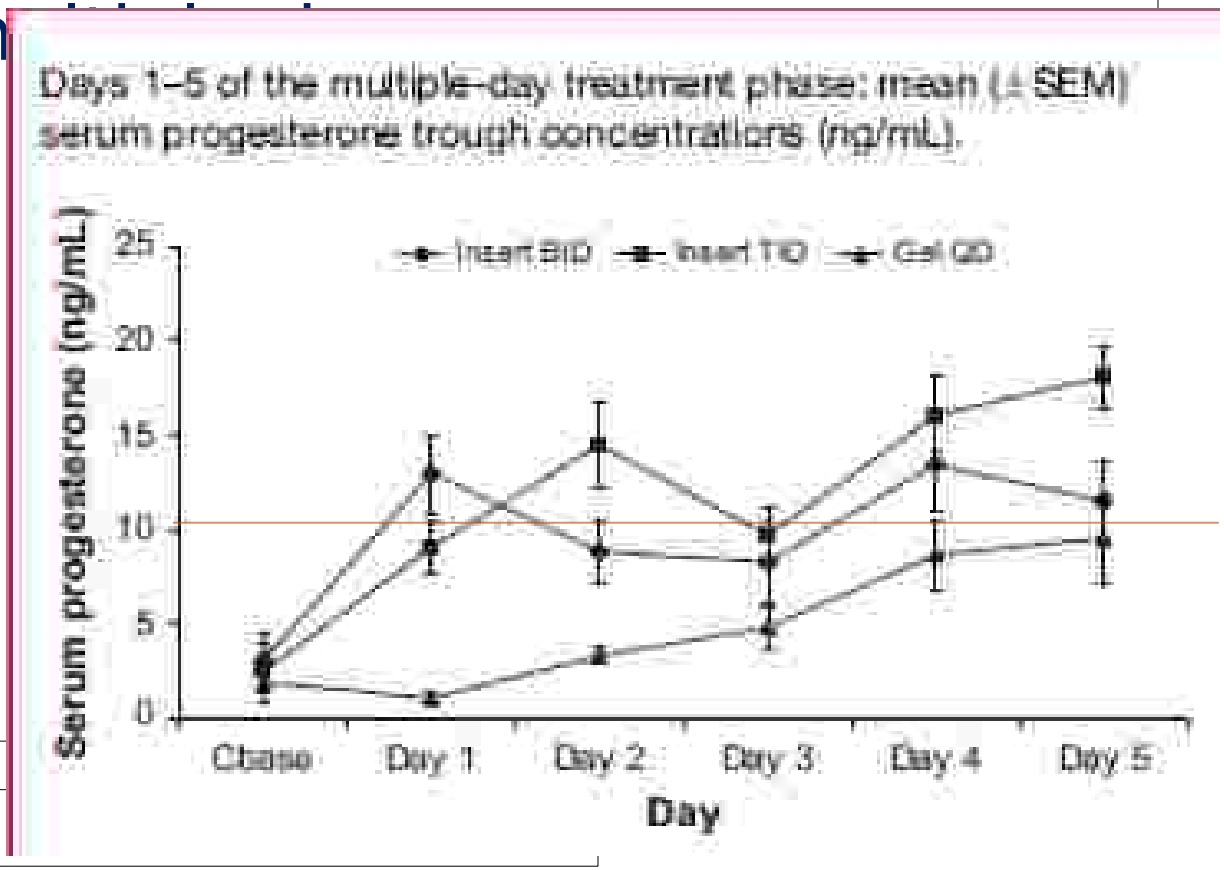


Blake. Endometrin vaginal progesterone PK study. Fertil Steril 2010.

Approach to Steady State

- Trough (predose) concentrations once per day
- During the m

Inserted group: 24~32 hours



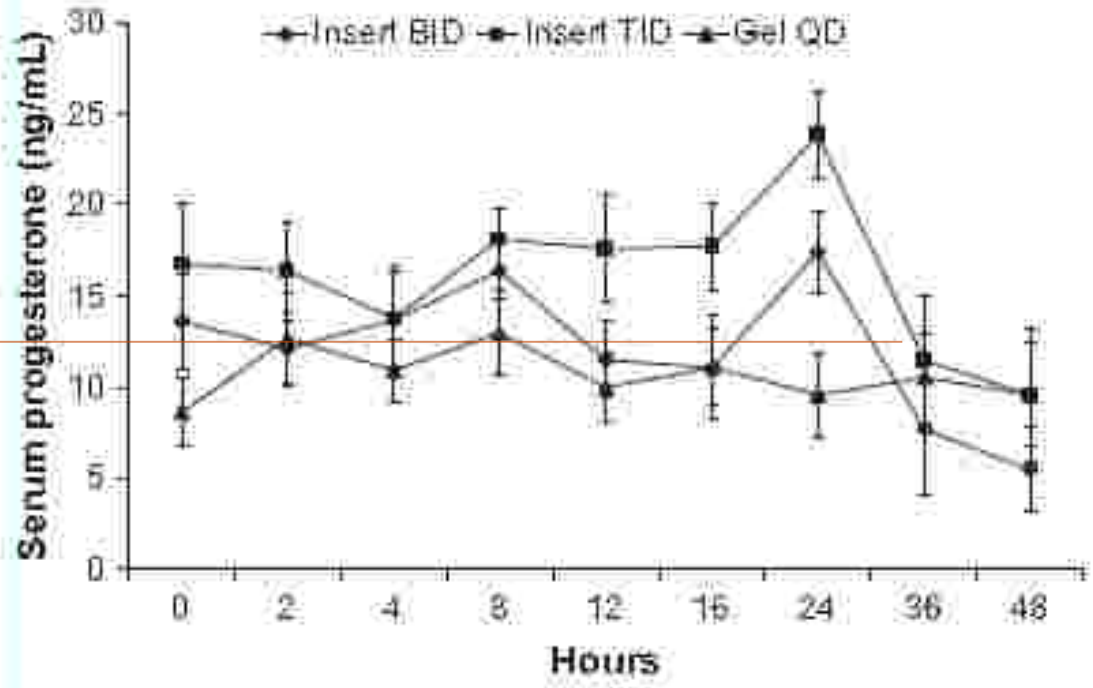
Multiple-day Treatment: day 5

- 24-hr period of D5:

Progesterone threshold associated with the midluteal phase

FIGURE 3

Day 6 of the multiple-day treatment phase: mean (±SEM) serum progesterone concentrations (ng/mL).



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Mean (±SEM) serum progesterone pharmacokinetic parameters

		Endometrin 100 mg bid (n=6) Mean ± SEM	Endometrin 100 mg bid (n=6) Mean ± SEM	Gel 90 mg qd (n=6) Mean ± SEM
		Single-dose treatment		
C_{max}	ng/mL	17.0 ± 2.7	19.0 ± 2.3	0.8 ± 1.39
T_{max}	h	24.0 ± 0.0	17.3 ± 3.2	13.3 ± 2.5
AUC (0–T)	ng•h/mL	88.4 ± 21.1	41.7 ± 16.5	80.9 ± 17.0
AUC (0-24)	ng•h/mL	217 ± 46	264 ± 68	81 ± 17.4
		Multiple-dose, multiple-day treatment, day 6		
C_{max}	ng/mL	16.5 ± 2.3	24.1 ± 2.2	14.3 ± 2.3
T_{max}	h	16.0 ± 3.8	18.0 ± 3.8	12.3 ± 6.2
C_{min}	ng/mL	8.9 ± 1.86	10.9 ± 2.7	7.4 ± 1.45
AUC (0–T)	ng•h/mL	157 ± 24	127 ± 14	264 ± 46
AUC (0-24)	ng•h/mL	327 ± 52	436 ± 43	264 ± 46
CL/F	L/h	657 ± 87	846 ± 112	417 ± 55

30% higher

2 x

Less than dose–proportional response

- **Random variability**
- **across most treatments in a previous study with Endometrin**

slow approach to steady state

variability

- Between-subject variability in day 5 pharmacokinetic parameters

=> Vaginal gel: Greatest Vaginal insert 3x/D: Least

- Coefficient of variation for Cmax on day 5

=> gel group: 39.7% Vaginal insert 3x/D: 23.2% Vaginal insert 2x/D: 29.9% (intermediate)

Decay phases

- 2 & 3 times daily
- ⇒ identical at 24 and 48 hours postdose
- The gel group:
- ⇒ Prolonged (concentrations decreased by only about a factor of four during the 48-hour observation period)
- ⇒ Slowed even further with repeated dosing
  - →by the end of the 5-day period
  - →No decay in serum progesterone concentration over the 36-hour window from 12 hours to 48 hours postdose

Safety Results

Serious AE encompass the following events

- Death, Life-threatening (i.e., at immediate risk of death), In-patient hospitalization or prolongation of existing hospitalization, Persistent or significant disability/incapacity, Congenital anomaly/birth defect

Safety Results

Total AES : 7 (no SAEs, mild in intensity)

- 1x headache (vaginal gel every day)
- 3x mild vaginal, during the washout phase (3 times a day), subsided after persisted progesterone use
  - Normal withdrawal bleeding, rather than breakthrough bleeding
- Abdominal pain, back pain, and rash
- All resolved without treatment within 3 to 4 days

DISCUSSION

- Pharmacokinetic profile of both dosage regimens of the vaginal insert formulation of progesterone compares favorably with the vaginal gel formulation
- Limitations
  - small sample size
  - considerable variability of plasma concentrations among the study subjects.
  - Variables such as Menstrual cycle/phase

Conclusion

- 2 dosage regimens of a novel vaginal insert formulation of progesterone can
- → achieve relatively high serum progesterone concentrations
- → reach steady state within 24 to 32 hours
- → maintain mean concentrations above 10 ng/mL.

- Endometrin vaginal insert formulations
- → Reached higher Cmax
- → Produced greater systemic exposure (AUC0–24)
- → Achieved steady state more rapidly
- → Leared more rapidly after termination of therapy than the comparator

THANK YOU FOR LISTENING!