Drug Interactions with Hormonal Contraceptives: Regulatory Perspective

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Disclaimer

- I have no conflicts of interest
- The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

Key Questions

- What should be used as the hormonal contraceptive (HC) drug-drug interaction (DDI) study endpoint, pharmacokinetics (PK) only or PK and pharmacodynamics (PD)? Why?

- Can we extrapolate a DDI study result from one progestin/estrogen to another? If so, under what circumstances?

- How do we define clinically meaningful DDIs based on PK or PK and PD assessments? How can we develop tangible and clear labeling recommendations?

Overview

- Introduction
- PK based DDI assessment and interpretation
- Approaches in PD based DDI assessment
- Data extrapolation
- Conclusion

Drug Interactions

Directions

- HC as a victim: Other drugs' effect on HC's PK, PD
- HC as a perpetrator: HC's effect on other drugs' PK, PD

Potential Concerns (HC as a victim)

- Induction: Exposure ↓ - Efficacy
- Inhibition: Exposure ↑ - Safety

Approaches

- Pharmacokinetics: AUC, C_{max}
- Pharmacodynamics: Progesterone, LH, FSH

Typical COC DDI Study Design

Single Dose Study (PK only)

Day 1 COC **PK**	Day 2-14 Washout	Day 15-29 Perpetrator	Day 30 Perpetrator + COC **PK**

In this case, perpetrator's steady state is reached by Day 29.

Multiple Dose Study: Lead-in + 2 cycles (PK + PD)

Cycle 1 (Lead-in)				Cycle 2 (Treatment A)				Cycle 3 (Treatment B)			
Week 1	Week 2	Week 3	Week 4 Pill free	Week 1	Week 2	Week 3	Week 4 Pill free	Week 1	Week 2	Week 3	Week 4 Pill free
COC only				**COC only** ↑ ↑ **PD PK**				**COC + Perpetrator** ↑ ↑ **PD PK**			

Sampling day for PD measurements will vary depending on analyte(s).
PK and PD measurements should be on the same day of each cycle for a cross-cycle comparison.

PK-based HC DDI Assessments

PK Assessment

- In general, PK parameters are used as the primary endpoint in HC DDI studies
- If C_{max} and AUC are within BE limits (90% CI: 80.00-125.00%), clinically meaningful DDIs are not expected

Case Example:

Interpreting PK-based HC DDI Study Results Outside of the BE Limits

PK DDI Interpretation Outside of BE Limits (1)

Rifampin DDI Study

- DNG/EV: 28-day, 4-phasic sequential COC containing dienogest (DNG) and estradiol valerate (EV)
- DNG: CYP3A4 substrate

- DDI study design with rifampin, a strong CYP3A4 inducer:
  - Days 1-11: DNG 3 mg/EV 2 mg
  - Days 12-16: DNG 3 mg/EV 2 mg + rifampin 600 mg QD

PK DDI Interpretation Outside of BE Limits (2)

- Study results:
  - DNG mean AUC: 83% ↓ = exposure of ~0.51 mg DNG
  - Estradiol (E2) mean AUC: 44% ↓ = exposure of ~1.1 mg E2
  - Mean C_{max} decreased: DNG (52%) and E2 (25%)
- Other information for consideration:
  - DNG: dose linear
  - Minimal dose for efficacy: 2 mg EV and 2-3 mg DNG for effective ovulation inhibition and sufficient cycle control
  - Note: We don't get this information unless the COC is an NME

DNG/EV Product Label

HIGHLIGHTS

Warning and Precautions

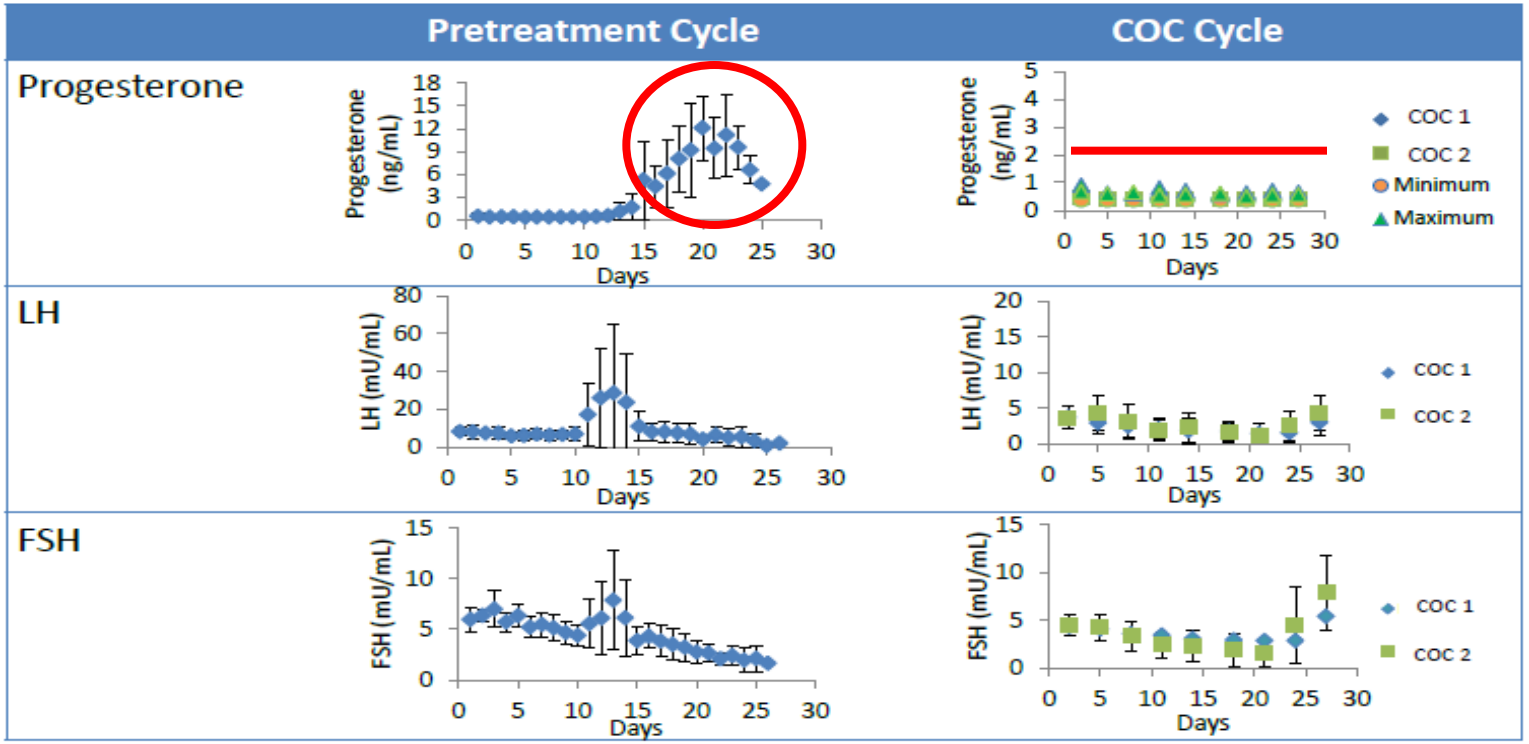
CYP3A4 induction: Women taking strong CYP3A4 inducers (for example, carbamazepine, phenytoin, rifampicin, and St. John's wort) **should not choose DNG/EV as their oral contraceptive** due to possibility of decreased contraceptive efficacy.

Exploring PD-based Assessment as a Supportive Approach to PK-based Assessment

PD Assessment (1)

- 33% of studies (1997-2013) conducted PD assessment in addition to PK

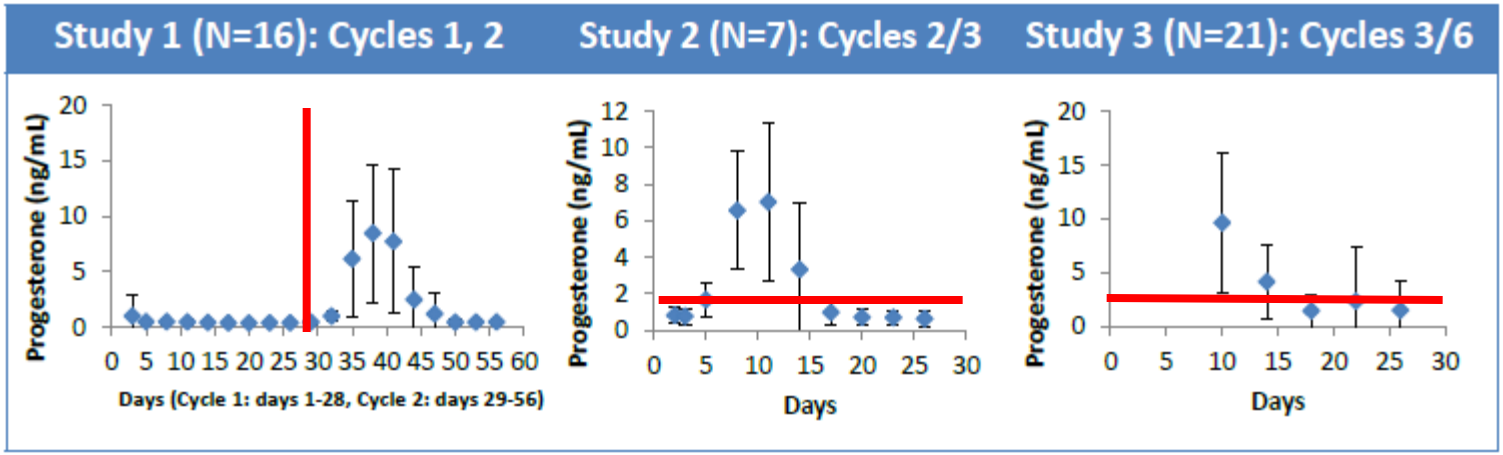
Progesterone, LH, and FSH Profiles: Pre-treatment vs. COC Cycles



- Progestrone may be a useful PD marker to determine the clinical relevance of DDI regarding efficacy, as it stays elevated for several days

PD Assessment (2)

Mean (SD) Progesterone concentrations in females with ovulation from Phase 2 ovulation studies or dose-finding studies



- Trend of progesterone surge with delayed ovulation was observed early in the next COC cycle in 3 clinical studies investigated
- Progesterone > 2 ng/mL with COCs might indicate ovulation
- Use of serum progesterone concentrations may be useful as a supportive PD indicator of DDI in addition to PK data

Case Examples:

Challenges in Data Extrapolation Between HCs

Case Examples

- Study 1: Boceprevir effect on **norethidrone (NET)/**ethinyl estradiol (EE)
  - NET 1 mg/EE 35 mcg (C 1-2) ± boceprevir 800 mg TID (C 3) (N=20)
- Study 2: **Boceprevir** effect on **drospirenone (DRSP)**/EE
  - DRSP 3 mg/EE 20 mcg (7 d) ± boceprevir 800 mg TID (7 d) (N=16)
- Study 3: **Ketoconazole (KTZ)** effect on DRSP/EE
  - DRSP 3 mg/EE 20 mcg (28 d) ± KTZ 200 mg BID (10 d) (N=22)

- Study 1 vs. 2: Same perpetrator on **different HC (progestin)**
- Study 2 vs. 3: **Different perpetrator** on same HC

Study 1 vs. Study 2: Boceprevir on NET/EE vs. DRSP/EE

PK results:

Study	Analyte	AUC GMR	AUC 90% CI	C_{max} GMR	C_{max} 90% CI
Study 1 (BOC)	NET	0.96	0.87-1.06	0.83	0.76-0.90
	EE	0.74	0.68-0.80	0.79	0.75-0.84
Study 2 (BOC)	DRSP	1.99	1.87-2.11	1.57	1.46-1.70
	EE	0.76	0.73-0.79	1.00	0.91-1.10

- No effect on NET but 99% ↑ on DRSP exposure
- EE exposure increase expected BUT 24-26% ↓ in AUC observed in both studies: The nature of boceprevir's effect on EE metabolism is not understood

Lin *et al*., *Eur J Clin Pharmacol* (2014); Kasserra *et al*., *CROI,* Boston, MA (2011)

Study 1: Boceprevir on NET/EE

PD results:

Parameter	GMR	90% CI
LH	0.73-0.88	0.43-1.50
FSH	1.13-1.25	0.83-1.71
Progestrone	Not reposrted	

Limitations of PD results in this study:

- Conflicting PD outcome: FSH ↑ vs. LH ↓
- Wide 90% CI: not powered adequately
- Absence of progesterone data
- Inconclusive PD results → example of challenge in PD utilization

Study 2 vs. Study 3: Boceprevir vs. KTZ on DRSP/EE

PK results:

	Analyte	AUC GMR	AUC 90% CI	C_{max} GMR	C_{max} 90% CI
Study 2 (BOC)	DRSP	1.99	1.87-2.11	1.57	1.46-1.70
	EE	0.76	0.73-0.79	1.00	0.91-1.10
Study 3)KTZ)	DRSP	2.68	2.44-2.95	1.97	1.79-2.17
	EE	1.40	1.31-1.49	1.39	1.28-1.52

- Increase in DRSP AUC observed in both studies: DRSP is a CYP3A4 substrate
- Both studies used same COC regimen → EE exposure increased (40%) in Study 3 as expected but decreased (24%) in Study 2

Kasserra *et al*., *CROI,* Boston, MA (2011); Wiesinger *et al*., *Br J Clin Pharmacol* (2015)

Data Extrapolation

Things to consider from the 3 COC DDI studies

- **Same perpetrator regimen** (boceprevir 800 mg TID), **Different progestins** (NET vs. DRSP), Same estrogen (EE) → **Different study outcome!**
  - NET: ↔ DRSP: 100% ↑
  - EE: 24-26% ↓
- **Different perpetrators** (strong CYP3A4 inhibitors: boceprevir 800 mg TID vs. KTZ 200 mg BID) on **same COC regimen** (DRSP 3 mg/EE 0.02 mg QD) → **Different study outcome**!
  - EE: 24% ↓ with boceprevir; 40% ↑ with ketoconazole
  - DRSP: 100-170% ↑ → shows that DRSP is a CYP3A4 substrate
- **Presents challenge in extrapolating DDI predictions from one to another COC** due to potentially different metabolic pathways, mechanism of interaction, or extent of the contribution from enzymes

Conclusions

- In general, PK parameters are used as the primary endpoint in HC DDI studies but often presents challenges in data interpretation for clinically meaningful DDIs
- Use of serum progesterone concentrations may be useful as a supportive PD indicator of DDI in addition to PK data with a caveat of potentially large variability, inconclusive or conflicting data and a need of large sample size
- There are challenges in extrapolating DDI predictions from one to another COC due to potentially different metabolic pathways, mechanism of interaction, or extent of the contribution from enzymes

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