Design and Interpretation of Oral Contraceptive Drug-Drug Interaction Studies

Vivek S. Purohit, Ph.D.,
Pfizer, Clinical Pharmacology,
Global Innovative Pharma Business Unit,
Groton, CT, USA.

Disclosure

Vivek S.Purohit is a fulltime employee and stockholder of Pfizer.

Acknowledgements

Pharmacokinetics, Dynamics and Metabolism

- David Rodrigues, Ernesto Callegari, Susanna Tse, Theunis Goosen

Clinical Pharmacology

- Jack Cook

Biostatistics

- Rob Labadie

Outline

- Summary of Pfizer (internal) guidance on “Oral Contraceptives (OC) Drug-Drug Interaction (DDI) Studies”
  - Design considerations for OC’s as victim (object)
    - Value of pharmacodynamic endpoints
  - Considerations for OC’s as perpetrators
- Pfizer experience with OC DDI studies
- Design and Interpretation Examples
- Summary

Current Understanding of OC DDI Potential

DDI Type	EE As Victim (Metabolized by CYP3A, CYP2C9, UGAT1A1, SULT1E1)	EE as Perpetrator (Very low EE hepatic levels during first pass)

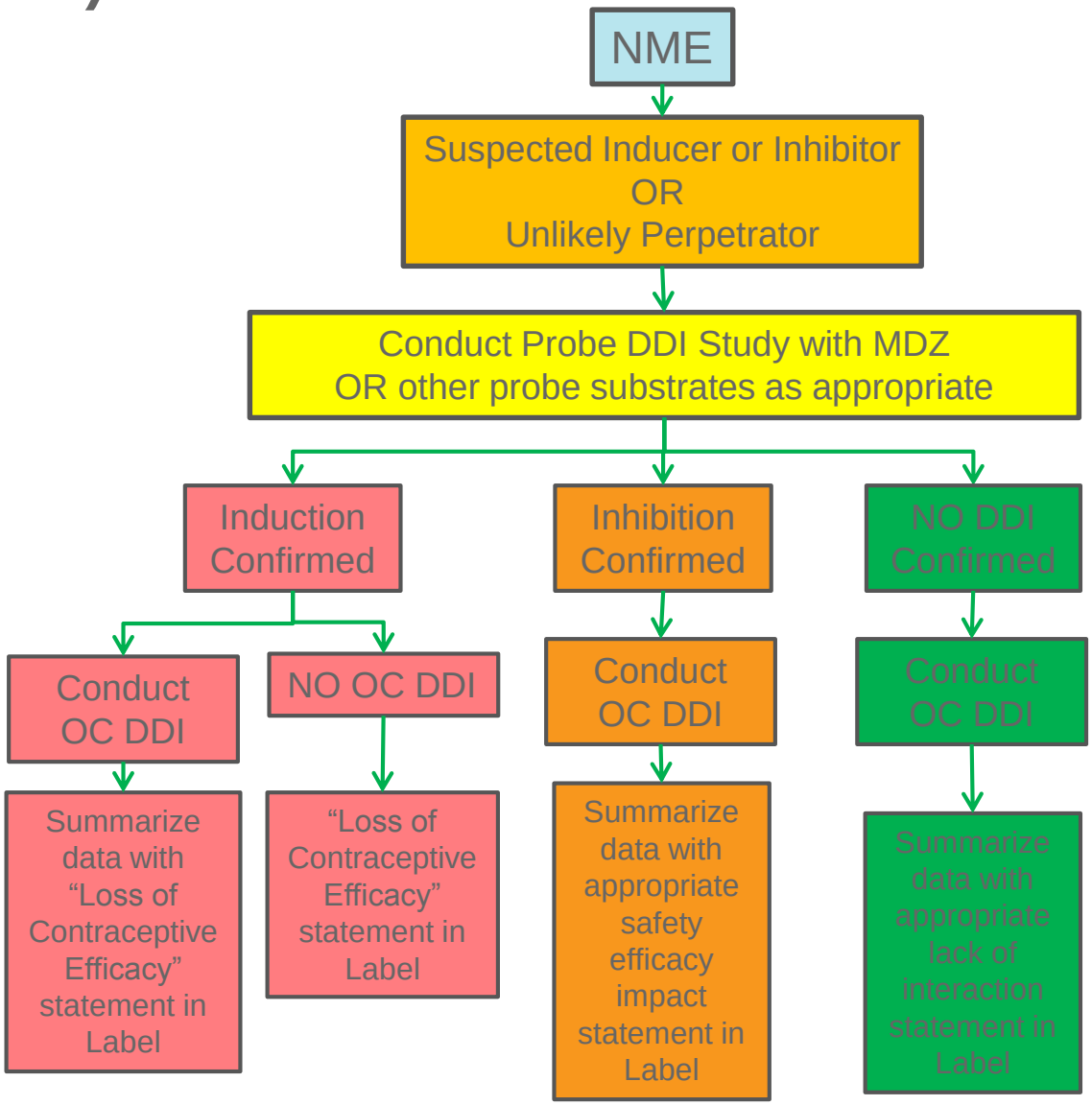
Induction	• Concerns regarding loss of efficacy and break through bleeding
	• Induction of CYP3A is the main focus
	  ○ especially moderate to strong inducers
	  ○ up to 65% decrease in EE AUC reported (rifampin)
	• Induction of CYP2C9, UGT, SULT enzymes are also possible
		• Not sure that this is an issue of clinical significance
		• Some evidence for CYP3A induction *in vitro*
		• Very low plasma levels of EE (<< EC_{50} for CYP3A induction)

Inhibition	• Most compounds increase EE AUC < 75%
	• Concerns regarding elevated C_{max} and CV effects
	• SULT1E1 plays a role in gut and liver first pass
	  ○ Inhibition of SULT1E1 (especially in gut) can increase EE AUC, C_{max}
	  ○ Etoricoxib only known inhibitor of SULT1E1 to date
	• Impact of potent CYP inhibition (CYP3A4 and/or CYP2C9) on EE PK not well studied
	  ○ not well differentiated vs. SULT1E1
	• Association of EE PK with *UGT1A1* genotype or inhibition not well studied
		• Evidence for inhibition of CYP2C19 and/or CYP1A1 clinically (gut CYP1A1 implicated)
		  ○ Higher first pass (low oral F) drugs that serve as CYP2C19 and CYP1A substrates elicit AUCR >2
		  ○ IVIVE not well established for CYP2C19 and CYP1A
		• Weak inhibitor of other CYPs
		  ○ Consistent with low [I]/Ki ratio
		• Evidence for mechanism-based inhibition of CYP3A *in vitro*
		  ○ K_{inact}, KI measurable but plasma levels very low.

EE = Ethinyl estradiol

Rationale for OC (Victim) DDI Studies

- Evidence from *in vitro* studies suggesting NME influences CYP3A activity.
- Target patient population for the NME will include females of childbearing potential who use oral contraceptives.
- The NME is a teratogen or likely to be co-administered or combined with a teratogen.
- Results from the OC DDI study will influence the design of clinical trials involving combination therapy during the drug development process.
- If *in vitro* data do not suggest a CYP3A interaction, and a claim of lack of DDI is still desired in the label, then a confirmatory clinical DDI study is needed.



NME = New molecular entity,

MDZ = Midazolam (Sensitive CYP3A substrate)

Study Design Considerations

- OC Dosing:
  - Single OC dose can be considered if induction or inhibition has been confirmed for NME using probe substrates
  - Multiple OC dosing can be considered for demonstrating lack of interaction
- NME dosed to steady state or up to 14 days if induction or TDI suspected
- Design options:
  - Open label, fixed sequence, single or multiple dose OC
  - Randomized, cross over with single or multiple dose OC
- Menstrual cycle considerations
  - Can be conducted without regard to the cycle if primarily looking to confirm a PK interaction
    - Metabolism via CYP3A not affected by menstrual cycle (*Clin Pharmacol Ther 1998 64: 268-277*)
  - If PD endpoints are collected, dosing synchronized with menstrual cycle is necessary

Study Population

- Healthy women subjects with exceptions for ethical considerations (e.g. Oncology)
- Post menopausal women
  - CYP3A induction similar between young (26±4) and postmenopausal (72±5) female subjects (*Clin Pharmacol Ther 2003 Sep;74(3):275-87*)
  - Low dose OCs have been shown to be safe for 1- 3 years (*Obstet Gynecol 2000, 95:87-94 ; Int J Fertil 1985, 30:15-28*)
- Women of child bearing potential can be considered specifically if PD assessments become necessary
- Healthy males NOT recommended
  - Females are more sensitive to hepatic CYP3A induction (*Clin Pharmacol Ther 2003 Sep;74(3):275-87*)
  - Inclusion of male subjects could underestimate the magnitude of interaction (*Clin Pharmacol Ther 2003 Sep;74: 525-535*)

Endpoint Considerations

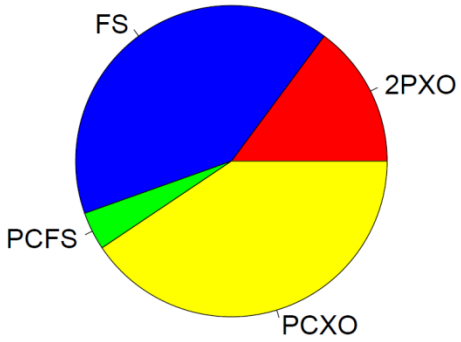
- PK Endpoints - AUC and C_{max}
- PK Criteria:
  - For claiming no interaction: 90% CI for GMR between 80 – 125 (Default)
    - Narrower or wider acceptance criteria may be considered on a case by case basis if justified, defined prospectively
- PD Endpoints – Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), progesterone and/or endosonography
  - Daily diaries for recording breakthrough bleeding
- PD Endpoints are not recommended routinely
  - Endpoints more variable limiting the ability to power a study based on PD endpoints as primary.
  - Changes in PD parameters difficult to detect and take longer to stabilize for making meaningful conclusions
  - PK is generally a more sensitive measure of CYP modulation than PD marker; we want to use the most sensitive marker for DDI studies
  - PD results unlikely to influence labeling if significant PK interaction observed.

OC's as Perpetrator of DDI

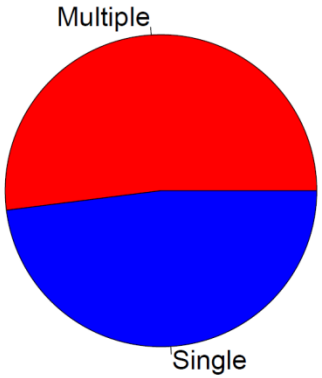
- Clinically significant DDI with OC's as perpetrators is rare but occurs
  - Examples – Selegeline, Tizanidine (NTI), Prednisolone
- Induction not usually of concern for OC's
- Inhibition of CYP2C19 or CYP1A may result in clinically significant DDI
- Design considerations are similar to OC's as victim

Pfizer Experience with OC DDI Studies (N=28*)

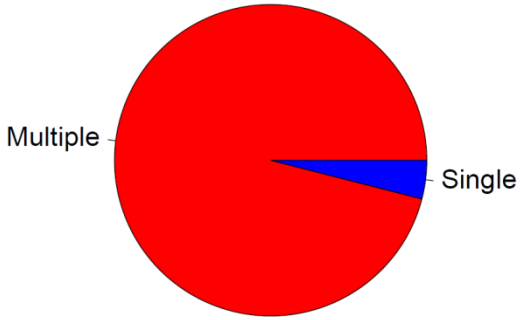
Study Design



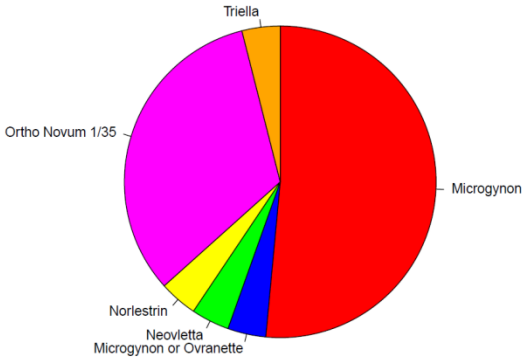
OC Dosing



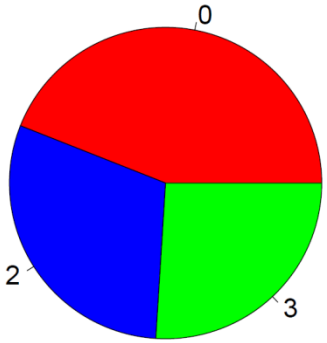
NME Dosing



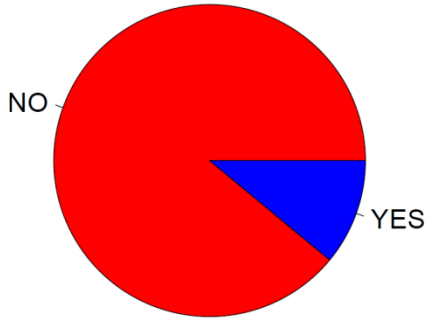
OC Brand



Study Conduct Over Number of Menstrual Cycles
(0 = Without regard to Menstrual cycle)



OC's As Perpetrators

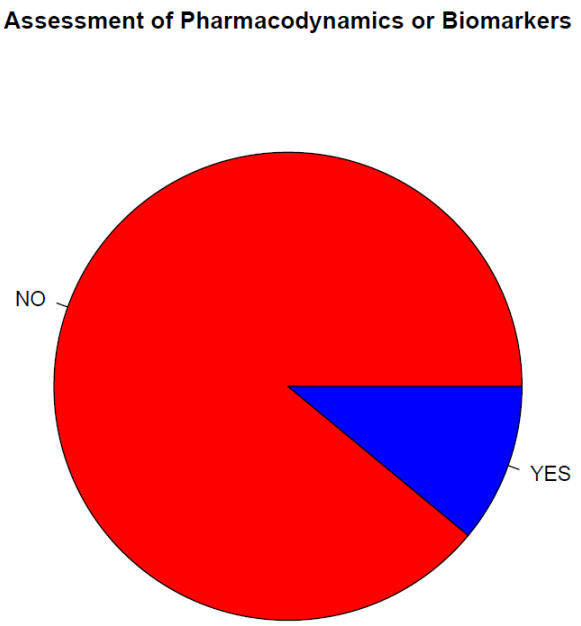


FS = Fixed sequence; PCFS = Placebo controlled fixed sequence; PCXO = Placebo controlled cross over; 2PXO = 2 Period cross over

* May not include all legacy studies prior to acquisition

Label Language Examples

1. Does not effect the PK of oral contraceptives.
2. No dose adjustments
3. No clinically significant drug-drug pharmacokinetic interactions were observed when drug X was administered with oral contraceptives (norethindrone/ethinyl estradiol).
4. Women of childbearing potential should use effective contraception during treatment. The co-administration of drug X with the oral contraceptive, Ortho-Novum® (35 mcg ethinyl estradiol and 1 mg norethindrone), results in an interaction between these two drugs, but is unlikely to reduce the contraceptive effect. Monitoring for adverse events related to oral contraceptives is recommended during co-administration.



No PD or biomarker data provided in labels.

It is unclear how PD data when available is being used to inform use of NME with OC's

Example 1: Design

Drug – Voriconazole

- Metabolized by CYP2C19, 2C9 and 3A4
- Strong CYP3A4 inhibitor
- Study designed to assess:
  - Voriconazole on OC's
  - OC's on Voriconazole
- Study design synchronized with menstrual cycle but no PD or Biomarker assessments

	Study period Period 1	Wash-out	Period 2	Wash-out	Period 3
Study day*	1–4	5–11	12–32	33–39	40–60
Menstrual cycle day	18–21	22–28	1–21	22–28	1–21
Voriconazole dosing	Day 1: 400 mg q12 h Days 2–3: 200 mg q12 h Day 4: 200 mg qAm	None	None	None	Day 57: 400 mg q12 h Days 58–60: 200 mg q12 h
Ortho-Novum® 1/35 dosing	None	None	Days 12–32: q24 h	None	Days 40–60: q24 h

*Serial pharmacokinetic sampling was conducted on study days 4, 32 and 60.

Br J Clin Pharmacol 2008, 65:4, 531-539

Example 1: Results and Interpretation

NME as Victim:

- Voriconazole exposure ↑ due to CYP2C19 inhibition

OC's as Victim:

- ↑ in exposures of both OC components consistent with CYP3A inhibition

Interpretation for Voriconazole:

- Magnitude of ↑ in exposures by OC's alone is unlikely to influence the adverse event profile for Voriconazole
- May be of concern in poor CYP2C19 metabolizers. Need for caution in these patients with appropriate AE monitoring

Interpretation for OC's:

- ↑ in exposures of OC's with Voriconazole are within the range of exposures observed for higher doses of OC's[a]. Need for appropriate AE monitoring necessary

Conclusion:

- Monitoring for AE due to Voriconazole and OC's is necessary when co administered
- For a drug like Voriconazole, the above results become important aid in developing monitoring guidelines for confirmatory studies (Phase 3 studies)

Pharmacokinetic parameter	% Ratio (90% CI)*
Voriconazole	
AUC_τ (ng h ml^{-1})	145.84 (132.13, 160.97)
C_{max} (ng ml^{-1})	114.30 (103.05, 126.77)
T_{max} (h)†	–‡
Ethinyl oestradiol	
AUC_τ (pg h ml^{-1})	160.68 (149.81, 172.35)
C_{max} (pg ml^{-1})	135.99 (127.67, 144.85)
T_{max} (h)†	–‡
Norethindrone	
AUC_τ (ng h ml^{-1})	153.39 (143.80, 163.62)
C_{max} (ng ml^{-1})	114.91 (103.05, 128.14)
T_{max} (h)†	–‡

[a] Br J Clin Pharmacol 1998; 46: 111-6 and Epilepsia 1999; 40:783-7

Br J Clin Pharmacol 2008, 65:4, 531-539

Example 2: Design, Results and Interpretation

- Drug - Maraviroc
- Metabolized by CYP3A
- Increased midazolam AUC and C_{max} by 18% and 21% respectively. Hence not a significant inducer or inhibitor of CYP3A
- Placebo controlled cross over trial without regard to menstrual cycle
- Study designed to rule out any induction of CYP3A which could reduce OC efficacy

Maraviroc 100 mg
or placebo
b.i.d. days 1–10
SD day 11
+
ethinyloestradiol 30 µg
levonorgestrel 150 µg
SD days 2–8

- Ethinyl Estradiol (EE) and Levonorgestrel (LN) levels not influenced by maraviroc

Treatment		AUC_t (pg ml^{-1} h)* mean (CV%)	C_{max} (pg ml^{-1})* mean (CV%)
EE	Maraviroc + EE/LN	745 (30)	84.0 (28)
	Placebo + EE/LN	746 (30)	84.8 (24)
	Ratio (%)‡ or difference§	99.6	98.4
	90% confidence interval	94.5, 105	91.3, 106
LN	Maraviroc + EE/LN	71 (24)	7.13 (19)
	Placebo + EE/LN	72 (28)	7.05 (22)
	Ratio (%)‡ or difference§	97.7	100
	90% confidence interval	92, 104	93, 108

*Unadjusted geometric means. †Unadjusted arithmetic means. ‡Ratio for AUC_{12} and C_{max}. §Difference for T_{max}; AUC_t was calculated for EE instead of AUC_t because some subjects did not have measurable EE concentrations up to 24 h postdose.

Interpretation:

- Although maraviroc does not impact OC levels, it is likely to be combined with drugs which are inducers of CYP3A and likely to reduce OC levels
- Hence, the use of maraviroc with OC's will be dictated by the drugs it is being combined with
- Study results become critical when a maraviroc like drug is used in monotherapy or in combination with other non-inducers

Br J Clin Pharmacol 2008, 65:1, 19-26

Induction Interpretation

- If an NME shows induction with a sensitive CYP3A substrate
- Further confirmed with OC DDI study
- OC's cannot be considered an effective method of contraception.
  - Alternate methods of contraception should be considered for future studies

- Question for consideration:
  - If induction by NME shown with sensitive CYP3A substrate is an OC DDI study necessary?

Summary

- Need for OC DDI studies should be based on results from probe (CYP3A) substrates (OC as victim) or representative inhibitor (CYP2C19) studies (OC as perpetrator)
- Confirmation of induction with a midazolam study can obviate the need for a dedicated OC DDI study
  - Label to indicate, OC's may not provide adequate contraception
- Confirmation of CYP3A inhibition or lack thereof with Midazolam may need to be followed by dedicated OC DDI study for label claim of adequate contraception and safety precautions if necessary
- PK criteria are adequate to establish DDI, establish usage guidelines and inform label
  - Focusing on PK criteria allows simplification of study design, resulting in shorter and focused studies
- PD endpoints are not routinely necessary and their value in developing usage guidelines or labeling is not clear

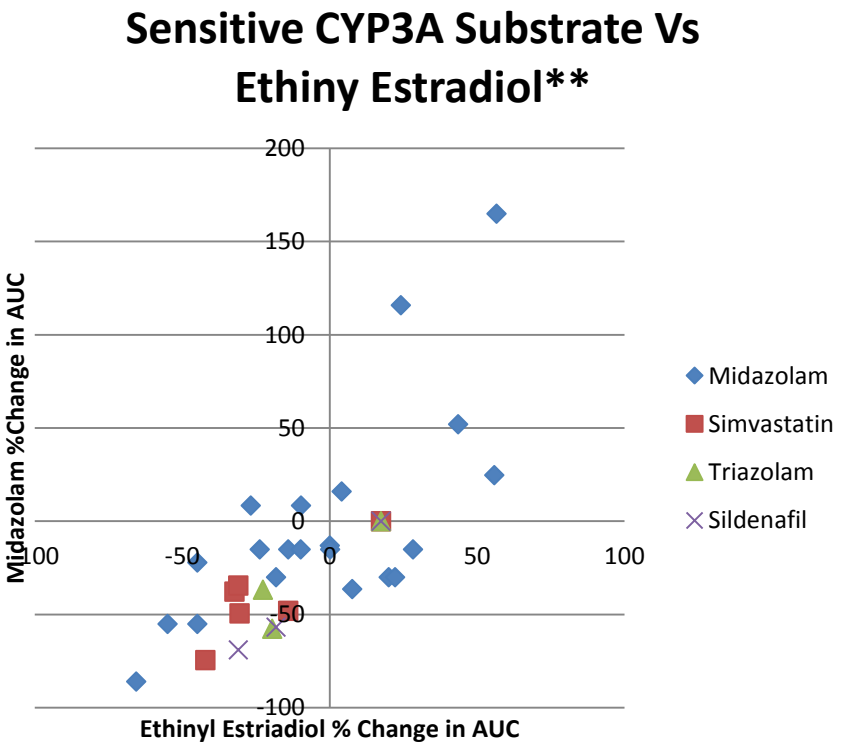
Summary (Cont'd)

- For drugs similar to voriconazole, to be used in populations likely to use oral contraceptives – dedicated OC DDI study conducted early can be useful in establishing monitoring guidelines for P3 study and provide adequate data for labeling
  - Any observed interaction (↑ in exposures of OC's) should be contextualized based on the totality of the safety data available and not just the data from DDI study
- Areas Future of Research:
  - Use of PBPK modeling to predict and assess DDI potential of NME's on OC's
  - Impact of biologics on OC's and understanding inflammatory disease drug interaction
    - Drugs like Actemra can alter CYP expression by altering the underlying disease and hence impact drug exposures

BACKUP SLIDES.

How do Midazolam Study Results Compare to Ethinyl Estradiol*

Just looking, at available data. Should be confirmed in a comprehensive analysis



* Data sourced from http://didb.druginteractioninfo.org/User/UserHome.aspx

** Removed two outliers (boceprevir and telaprevir)

Effect of Menstrual Cycle Phase on CYP3A activity.

- Midazolam (0.025 mg/kg) was administered intravenously to 10 white premenopausal female volunteers during the midfollicular and midluteal phases of the menstrual cycle for 3 complete cycles. Serum was collected for a 6-hour period, and enzyme activity was represented by midazolam plasma clearance.
- No difference in clearance was observed during the menstrual cycle phases. Mean +/- SD midazolam clearance was 0.00816 +/- 0.00252 L/min/kg during the midfollicular phase and 0.00818 +/- 0.00224 during the midluteal phase (P value = 0.96).

Clin Pharmacol Ther 1998 64: 268-277