Drug interaction with Oral Contraceptives-
considerations for study design and data interpretation

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Disclosures

- Haiying Sun and Venkateswar Jarugula are full time employees of Novartis Institutes for BioMedical Research, East Hanover, NJ

- Haiying Sun and Venkateswar Jarugula are stockholders in Novartis
Outline

- Clinical relevance of oral contraceptives (OCs) drug-drug interactions
- Oral Contraceptive use world-wide
- Drug metabolism characteristics of Oral Contraceptives
- Sex Hormone Binding Globulin (SHBG) and its effect on OCs
- PK/PD based OC DDI study-case example
- NCE impact on progestins
- Review of labeling information
- Summary of study design and interpretation considerations
Information considered to initiate clinical OC DDI study

OCs as victim drugs

• Clinical program considers the Benefits/Risks when including women of child bearing potential
  • especially when reproductive toxicity studies are not completed or compound is teratogenic
• The level of contraception (highly/acceptable effective) depends on reproductive toxicity and genotoxicity of the NCE
• Whether OC can be used as one of the contraceptive method depends on DDI assessment outcome

- Understanding of *in vitro* findings
  • DDI potential of NCE (CYP3A4/ UGT1A1/CYP2C19/CYP2C9 )

- A consideration of *in vivo clinical* DDI findings
  • Eg In vivo CYP3A4 probe study with Midazolam, if available

- A consideration of teratogenic findings
  • A potential human teratogen needs to be studied *in vivo* for effects on contraceptive steroids if the drug is intended for use in fertile women, regardless of *in vitro* induction study results.
Use of COCs Worldwide

- Ethinyl estradiol is the common component of most COCs
- Progestins:
  - Global total: Levonorgestrel and drospirenone are most commonly used
  - Regional differences exist:
    - USA – Norethindrone and norgestimate more commonly used than in other countries
    - China – Desogestrel (73% of total volume)
    - Italy – Gestodene (33% of total volume)
## Drug Metabolism Characteristics of OCs

<table>
<thead>
<tr>
<th>Compound</th>
<th>Phase I Metabolism</th>
<th>Phase II Metabolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethinyl estradiol</td>
<td>CYP3A4 (major), CYP2C9 (minor)</td>
<td>SULT1E1 (major) UGT1A1 (minor)</td>
</tr>
<tr>
<td>Drospirenone</td>
<td>CYP3A4 (?)</td>
<td></td>
</tr>
<tr>
<td>Norgestimate (Pro-drug)</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Norelgestromin (17-deacetyl norgestimate)</td>
<td>CYP3A4</td>
<td>Glucuronidation &amp; sulfation</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Desogestrel (Pro-drug)</td>
<td>CYP2C9, CYP2C19</td>
<td></td>
</tr>
<tr>
<td>3-ketodesogestrel</td>
<td>CYP3A4</td>
<td></td>
</tr>
<tr>
<td>Norethindrone</td>
<td>CYP3A4, 2C19</td>
<td></td>
</tr>
<tr>
<td>Gestodene</td>
<td>CYP3A4</td>
<td>Glucuronidation</td>
</tr>
</tbody>
</table>

Pathways relevant for OC as a victim drug: CYP3A4/ UGT1A1 /CYP2C19/2C9
Sex Hormone Binding Globulin (SHBG) and its effect on OCs

- Progestins binds to low capacity, high affinity receptors on SHBG

- Impact of SHBG elevation on free drug concentration of progestins has not been well studied
- Progestin total exposure correlates with SHBG levels (Norethindrone, Levonorgestrel, 3-ketodesogestrel and gestodene)
- Time-dependent progestin PK for total AUC due to EE-mediated SHBG induction
- Multiple dose OC can be considered for DDI studies involving SHBG bound progestins
- The single dose PK study design can be considered for low SHBG binding progestin
Is PD characterization needed for OC DDI studies?

- **When to include PD measurement in the OC interaction study?**

PD information may be helpful in some scenarios:

- NCE has relevant PD interaction mechanism that may alter hormone levels (e.g., drugs for reproductive conditions, CNS drugs that may alter hormone production)

- PD endpoints serve as supportive information of maintained efficacy in spite of observed PK changes (however, published studies rarely have power to be definitive)
Case study with PK/PD component

- NCE is an oral agent for the treatment of Cystic Fibrosis
- EE 30ug/ LVG150 ug
- Single sequence, two-treatment period study (21 days/period)
- Synchronized for 3 OC cycles if not already on OC
- In healthy premenopausal female volunteers
- Powered based on PK variability (n= 45 enrolled)

![Graphs showing PK/PD relationship for Ethinyl estradiol and Levonorgestrel in OC alone and OC+NCE conditions.](image-url)
Pharmacodynamic measurements

<table>
<thead>
<tr>
<th>PD parameters</th>
<th>Median (range)</th>
<th>OC</th>
<th>OC+NCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol (pg/mL)</td>
<td>20 (20-73.4)</td>
<td>23.5 (20-98)</td>
<td></td>
</tr>
<tr>
<td>Follicle size (mm)</td>
<td>5.40 (3.8 -18.1)</td>
<td>6.30 (0.0 - 23.0)</td>
<td></td>
</tr>
<tr>
<td>Hoogland score (score=4)</td>
<td>1 (1)</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

Progesterone level remains < 2ng/mL
Higher levels seen in mid cycle FSH/LH levels, minimal changes in other PD endpoints

Study concluded based on PK findings
Challenges of PD data interpretation

- PK data drives the conclusions when interpreting OC DDI outcome

- For PD data as an endpoint to be included, convincing PD criteria need to be established for meaningful results interpretation
  - Determination of occurrence of ovulation is a composite assessment
  - PD endpoints and sampling points vary among studies
  - Clinical interpretation of data may differ amongst investigators
Norethindrone and Levonorgestrel are well studied.
Most of the studies showed clinical PK DDI < 20% changes.

*University of Washington, Drug interaction database program*
## Progestin exposure increase due to inhibition

<table>
<thead>
<tr>
<th>Inhibition increase in AUC&gt;20%</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>norethindrone</td>
<td>Voriconazole: 49%↑&lt;br&gt;Protease inhibitor: 50%↑most</td>
</tr>
<tr>
<td>levonorgestrel</td>
<td>Faldaprevir: 44% ↑most&lt;br&gt;Netupitant and palonosetron: 41%↑</td>
</tr>
<tr>
<td>norelgestromin (Norgestimate active metabolite)</td>
<td>Elvitegravir/cobicistat/&lt;br&gt;Emtricitabine/tenofovir: 126%↑&lt;br&gt;Lopinavir and ritonavir: 83%↑</td>
</tr>
<tr>
<td>3-ketodesogestrel (Desogestrel active metabolite)</td>
<td>Itraconazole: 72%↑</td>
</tr>
</tbody>
</table>

- PK changes do not always correlate with CYP3A4 inhibition; Change is generally small
- Inhibitors affect multiple enzymes: eg voriconazole
- Newer progestin drospirenone (Spironolactone analog): 2.5-fold change by ketoconazole reported
Progestin exposure decrease due to induction

<table>
<thead>
<tr>
<th></th>
<th>Norethindrone</th>
<th>Levonorgestrel</th>
<th>Norelgestromin</th>
<th>3-ketodesogestrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine 600 mg daily</td>
<td>↓ 57%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz 600 mg daily</td>
<td></td>
<td>↓59%</td>
<td>↓64%</td>
<td></td>
</tr>
<tr>
<td>St John’s Wort 300 mg bid</td>
<td></td>
<td>↓(11%)*</td>
<td></td>
<td>↓42%</td>
</tr>
</tbody>
</table>

- Limited comparisons suggest extent of induction by CYP3A4 inducers are qualitatively comparable (i.e. similar trend)
- Another OC study may be necessary if unexpected result is seen (as compared to *in vitro* or other *in vivo* results)

*In the study, oral midazolam clearance only increased by 52% by this St John’s wort ext*
Review of Labeling Information

- Labeling information & literature reports of DDI studies for drugs commonly known to be inducers or inhibitors of COCs were reviewed (eg: antiepileptics, antivirals and antibiotics). Trends are captured below.

What type of study was conducted? (PK or PK/PD; single or multiple dose)

- No consistent pattern for types of studies (PK or PK/PD, SD or MD) regardless of their inhibition/induction potential

What information is used in the label? (PK data, PK/PD data or general text about inhibition/induction potential of NCE)?

- Inclusion of PD data rare but exists in the DDI section (eg: felbamate)
- Older drugs: Inhibition/induction potential of NCE mentioned, without any data
- Newer drugs: PK information included

Does the recommendation (use of additional contraceptive methods) differ based on magnitude of observed induction or the pregnancy category of the drug?

- Drugs in pregnancy categories ‘C’ & ‘D’ (US labels) include a recommendation to use additional methods of contraception, irrespective of the magnitude of interaction
- Drugs in pregnancy category ‘X’ include a recommendation for alternate methods of contraception
Summary

- The need for multiple dose OC PK measurement depends on PK characteristics including SHBG binding;

- Single and multiple dose PK-only studies are recommended as default in view of challenges associated with PD data interpretation;

- OC DDI extrapolation considerations
  - Lack of significant inhibition interactions on the progestin component, especially for those well studied progestins
  - Shared CYP3A4 pathways and the observed effect of 3A4 induction
  - A understanding of NCE inhibition/induction profile
Acknowledgement

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