A Regulatory Perspective On the Utilization of Cocktail Approach In Assessing Drug Interactions

Lei Zhang, Ph.D.

Special Assistant to Office Director
Office of Clinical Pharmacology (OCP)
OTS, CDER, FDA

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American Association of Pharmaceutical Scientists Annual meeting
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PubMed Search on Nov 12, 2010:
using “Cocktail and drug interaction and human”
-138 results (1973-2010) (also include in vitro cocktail approach)
-11 publications in 2010
-12 publications in 2009
-12 publications in 2008
25% in the most recent 3 years
7 using drug cocktail/1,681 drug interaction trials (0.4%)
Why Cocktail?

• Utility:
  – An efficient *in vivo* screening tool on drug interaction potential of new molecular entities as inhibitors or inducers
    • Study effect on multiple enzymes or transporters simultaneously rather than multiple single-pair studies
      – Confirm *in vitro* drug interaction assessments
      – Suggest additional in vivo DDI studies
  – Can be used where in vitro assays may not be well established, e.g.,
    • Herbal products
    • Therapeutic proteins

• Challenges:
  – Ideal probe substrates may not be dosed together with other probes
    • Potential PK and/or PD interaction
    • Tolerability/safety
  – Further *in vivo* DDI studies may be needed to provide quantitative exposure changes for labeling purpose
  – Analytical assay challenges
    • Multiple moieties (substrates plus their metabolites) will need to be assayed
Simultaneous administration of a mixture of substrates of CYP enzymes in one study (i.e., a "cocktail approach") in human volunteers is another way to evaluate a drug's inhibition or induction potential, provided that the study is designed properly and the following factors are present: (1) the substrates are specific for individual CYP enzymes; (2) there are no interactions among the substrates; and (3) the study is conducted in sufficient number of subjects (see section IV.G). Negative results from a cocktail study can eliminate the need for further evaluation of particular CYP enzymes. Positive results can indicate the need for further in vivo evaluation to provide quantitative exposure changes (such as AUC, Cmax), if the initial evaluation only assessed the changes in the urinary parent to metabolite ratios. The data generated from a cocktail study can supplement data from other in vitro and in vivo DDI information including PBPK modeling and simulation data.

**Study Design:**
- Substrates are specific and "sensitive"
- No interaction between substrates
- Sufficient number of subjects

**Data Interpretation:**
1. Negative results
2. Positive results
3. Not stand alone (supplement to other *in vitro* or *in vivo* DDI information including PBPK modeling and simulation data)
The potential of an investigational drug to inhibit or induce the metabolism of other drugs should be investigated. Usually the investigation is initiated by *in vitro* studies and those studies are followed by *in vivo* studies if the *in vitro* data show that an effect *in vivo* cannot be excluded. However, it is also possible to study the effects directly *in vivo*, e.g. by the use of cocktail studies (see section 5.4.2).

It is possible to use so-called "cocktail studies" investigating the inhibitory or inducing effect of an investigational drug on several enzymes in one *in vivo* study. In this case, it should have been demonstrated *in vivo* that the probe drugs combined in the "cocktail" do not interact with each other. The doses used should preferably be the doses used in this validation. Deviations from this should be justified. Full characterisation of the plasma concentration-time curves of the probe drug is recommended, estimating the effect on (oral) clearance. Use of metabolite to parent drug concentration ratios in plasma or urine is not recommended. If satisfactorily performed, the results of the cocktail studies can be extrapolated to other drugs and be used to support treatment recommendations of the SmPC.
### Some Review Examples at the FDA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Purpose</th>
<th>Cocktail Selection</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>In vitro data show that Drug A has inhibition potential on CYP1A2, CYP3A4, CYP2C9, and CYP2C19, i.e., I/Ki &gt; 0.1.</td>
<td>-Customized (4-probe) cocktail: simvastatin (CYP3A), caffeine (CYP1A2), omeprazole (CYP2C19), and diclofenac (CYP2C9)</td>
</tr>
</tbody>
</table>
| B    | In vitro studies show that Drug B has inhibition potential on CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A4, i.e., I/Ki>0.1. | -Cooperstown 5+1 cocktail (CYP1A2, 2C9, 2C19, 2D6, 3A4)  
- A separate DDI study with a CYP2B6 substrate |
| C    | A herbal product, in vitro drug interaction study may not be predictive; Use cocktail as a screen to determine its in vivo interaction potential. | -Cooperstown 5+1 cocktail (CYP1A2, 2C9, 2C19, 2D6, 3A4) |
| D    | Therapeutic protein, in vitro drug interaction may not be predictive of in vivo DDI; Use cocktail as a screen to determine its in vivo interaction potential. | -Cocktail to cover major CYP enzymes |
Approved Drug Examples

• Tipranavir (post-marketing commitment (PMC))
• Pazopanib (original submission)
Case 1: Tipranavir/Ritonavir (TPV/r)

CYPs
- *In vitro* effect of TPV
  - TPV is a CYP3A inducer and inhibitor.
  - TPV is an inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP2D6.
- *In vivo* studies conducted: CYP3A
  - In vivo effect of TPV/r (500/200 mg bid) on CYP3A is inhibition
- *What is in vivo effect of TPV/r on CYP1A2, 2C9, 2C19 and 2D6 substrate drugs?*

Transporters
- No *in vitro* study was conducted for inhibition or induction effect on P-gp
- *In vivo* effect of TPV/r on P-gp transporter is induction
  - Loperamide interaction study
  - Protease inhibitor interaction data
  - ADME study with $^{14}$C-TPV/r
  - Clarithromycin interaction study
- *What is in vivo effect of TPV/r on digoxin?*

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/21814_000_Aptivus_biopharmr1.pdf
Post-Marketing Commitment (PMC)
Tipranavir/Ritonavir

17. Conduct a CYP/P-gp mechanistic study to determine effect of tipranavir/ritonavir on individual CYPs.

Protocol Submission: September 30, 2005
Final Report Submission: December 31, 2006

The sponsor took a cocktail approach to fulfill this PMC.
Tipranavir/Ritonavir
-A PMC Cocktail Study

• **Purpose:**
  – Study net effect of TPV/r on various CYP probe substrates and digoxin.

• **Cocktail:** (Modified “Cooperstown 5 + 1 cocktail”)
  – Oral (p.o.) caffeine (1A2, NAT-2, and XO), warfarin (2C9) + vitamin K, omeprazole (2C19), dextromethorphan (2D6), and midazolam (3A) (i.v. and po)
  – Digoxin (P-gp) (p.o. and i.v.)
    • Dosed separately. Its compatibility with the “cooperstown cocktail” is not known.
  – Genotype information was collected
    • Effect of gene variants of CYP2C9, 2C19, and 2D6 on drug interaction was explored.
      – Limited sample size.

*<Dumond JB, et. al., Clin Pharmacol Ther. 87(6):735-42, 2010>*
Tipranavir/Ritonavir - A PMC Cocktail Study (2)

<table>
<thead>
<tr>
<th>Enzyme of Interest</th>
<th>Exposure after Single Dose (SD) TPV/r</th>
<th>Exposure after Multiple Dose (MD) TPV/r</th>
<th>Implication</th>
</tr>
</thead>
</table>
| P-gp (digoxin)    | ↑                                    | ↔                                     | SD: P-gp inhibitor  
|                   |                                      | MD: P-gp inducer                      |
| CYP1A2 (caffeine) | ↔                                    | Modest ↓                              | Modest CYP1A2 inducer |
| CYP2C9 (warfarin) | ↔                                    | ↔                                     | No effect on CYP2C9 |
| CYP2C19 (omeprazole) | Modest ↑                           | Marked ↓                             | SD: CYP2C19 inhibitor  
|                   |                                      | MD: CYP2C19 inducer                    |
| CYP2D6 (dextromethorphan) or CYP3A (midazolam) | ↑                                    | ↑                                     | CYP2D6 inhibitor  
|                   |                                      |                                        | CYP3A inhibitor |
1. APTIVUS co-administered with 200 mg of ritonavir at the recommended dose, is a net inhibitor of CYP 3A and may increase plasma concentrations of agents that are primarily metabolized by CYP 3A. Thus, co-administration of APTIVUS/ritonavir with drugs highly dependent on CYP 3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events should be contraindicated. Co-administration with other CYP 3A substrates may require a dose adjustment or additional monitoring (see CONTRAINDICATIONS and PRECAUTIONS).

2. Studies in human liver microsomes indicated tipranavir is an inhibitor of CYP 1A2, CYP 2C9, CYP 2C19 and CYP 2D6. The potential net effect of tipranavir/ritonavir on CYP 2D6 is inhibition, because ritonavir is a CYP 2D6 inhibitor. The in vivo net effect of tipranavir administered with ritonavir on CYP 1A2, CYP 2C9 and CYP 2C19 is not known. Data are not available to indicate whether tipranavir inhibits or induces glucuronosyl transferases and whether tipranavir induces CYP 1A2, CYP 2C9 and CYP 2C19.

3. Tipranavir is a P-gp substrate, a weak P-gp inhibitor, and appears to be a potent P-gp inducer as well. Data suggest that the net effect of tipranavir co-administered with 200 mg of ritonavir is P-gp induction at steady-state, although ritonavir is a P-gp inhibitor.

4. It is difficult to predict the net effect of APTIVUS administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp. The net effect will vary depending on the relative affinity of the co-administered drugs for CYP 3A and P-gp, and the extent of intestinal first-pass metabolism/efflux.
Tipranavir/Ritonavir -Labeling

• Labeling was modified based on the results from the study.

7. Drug Interactions

7.2 Potency

A phenotypic cocktail study was conducted with 16 healthy volunteers…

Potent inhibition of CYP 2D6 and both hepatic and intestinal CYP 3A4/5 activities were observed after first dose and steady state.

The digoxin results indicate P-gp was inhibited after the first dose of APTIVUS/ritonavir followed by induction of P-gp over time. Thus, it is difficult to predict the net effect of APTIVUS administered with ritonavir on oral bioavailability and plasma concentrations of drugs that are dual substrates of CYP 3A and P-gp…
Case 2: Pazopanib

A tyrosine kinase inhibitor indicated for the treatment of patients with advanced renal carcinoma.

- In vitro data showed that pazopanib inhibited multiple CYP enzymes.

<table>
<thead>
<tr>
<th>CYP</th>
<th>IC_{50} (μM)</th>
<th>Cmax/IC_{50}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>16</td>
<td>8.3</td>
</tr>
<tr>
<td>2B6</td>
<td>15</td>
<td>8.9</td>
</tr>
<tr>
<td>2C8</td>
<td>10</td>
<td>13.3</td>
</tr>
<tr>
<td>2C9</td>
<td>7.9</td>
<td>16.8</td>
</tr>
<tr>
<td>2C19</td>
<td>11</td>
<td>12.1</td>
</tr>
<tr>
<td>2D6</td>
<td>18</td>
<td>7.4</td>
</tr>
<tr>
<td>2E1</td>
<td>17</td>
<td>7.8</td>
</tr>
<tr>
<td>3A4</td>
<td>12</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Mean C_{max} ~133 μM (76-209 μM) (800 mg QD).

- In vitro data also showed that pazopanib induced CYP3A4 and CYP2B6 but not CYP1A2 at clinically relevant concentrations.

Case 2: Pazopanib (2)

- Cocktail approach to investigate whether pazopanib show in vivo inhibition or induction on major CYP enzymes
  - Modified Cooperstown 5+1 cocktail in patients with advanced solid tumors
    - Midazolam (CYP3A), warfarin (CYP2C9), omeprazole (CYP2C19), caffeine (CYP1A2), and dextromethorphan (CYP2D6)
    - Genotype information was collected
- A separate study with paclitaxel for effect on CYP2C8.

BC Goh, et. al., Clin Pharm Ther, 88: 652-659, 2010
**Case 2: Pazopanib (3)**

**Table 20.** Effect of pazopanib on the metabolic activities of CYP (3A4, 2C9, 2C19, 1A2, and 2D6).

<table>
<thead>
<tr>
<th>Analyte(s)</th>
<th>Parameter</th>
<th>N</th>
<th>Ratio of Geometric Least Squares Means</th>
<th>90% CI for the Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (CYP34)</td>
<td>AUC(0-∞) (ng.h/mL)</td>
<td>14</td>
<td>1.32</td>
<td>1.11, 1.57</td>
</tr>
<tr>
<td>1-hydroxymidazolam</td>
<td>AUC(0-1) (ng.h/mL)</td>
<td>21</td>
<td>1.27</td>
<td>1.06, 1.53</td>
</tr>
<tr>
<td>S-Warfarin (CYP2C9)</td>
<td>AUC(0-∞) (ng.h/mL)</td>
<td>9</td>
<td>0.82</td>
<td>0.64, 1.06</td>
</tr>
<tr>
<td>Omeprazole/5-hydroxyomeprazole (CYP2C19)</td>
<td>Concentration ratio at 2 hours</td>
<td>12</td>
<td>0.92</td>
<td>0.61, 1.37</td>
</tr>
<tr>
<td>Caffeine (CYP1A2)</td>
<td>AUC(0-10)</td>
<td>20</td>
<td>1.00</td>
<td>0.77, 1.30</td>
</tr>
<tr>
<td>Urine Dextromethorphan to 1-Dextorphan Ratio (CYP2D6)</td>
<td>Concentration ratio 0-4 hours</td>
<td>16</td>
<td>1.33</td>
<td>0.99, 1.77</td>
</tr>
<tr>
<td></td>
<td>Concentration ratio 4-8 hours</td>
<td>15</td>
<td>1.64</td>
<td>1.16, 2.32</td>
</tr>
<tr>
<td></td>
<td>Concentration ratio 8-10 hours</td>
<td>17</td>
<td>1.62</td>
<td>1.13, 2.34</td>
</tr>
<tr>
<td></td>
<td>Concentration ratio 10-24 hours</td>
<td>17</td>
<td>1.45</td>
<td>1.02, 2.07</td>
</tr>
</tbody>
</table>

**Table 22.** Effect of pazopanib on paclitaxel clearance and Cmax.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>N</th>
<th>Geometric Least Squares Mean</th>
<th>Ratio</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr/m²)</td>
<td>17</td>
<td>Day 1 (Paclitaxel)</td>
<td>21.7</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 15 (Paclitaxel + Pazopanib)</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>Cmax (µg/mL)a</td>
<td>20</td>
<td>Day 1 (Paclitaxel)</td>
<td>0.427</td>
<td>1.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 15 (Paclitaxel + Pazopanib)</td>
<td>0.560</td>
<td></td>
</tr>
</tbody>
</table>

**BC Goh, et. al., Clin Pharm Ther, 88: 652-659, 2010**

Case 2: Pazopanib (4) --Labeling

Highlights:

**CYP Substrates:** Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. (7.2)

7.2 Effects of Pazopanib on CYP Substrates

Results from drug-drug interaction studies conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19 [see Clinical Pharmacology (12.3)].

Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events. [See Clinical Pharmacology (12.3).]
12. Clinical Pharmacology

In vitro studies with human liver microsomes showed that pazopanib inhibited the activities of CYP enzymes 1A2, 3A4, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1. Potential induction of human CYP3A4 was demonstrated in an in vitro human PXR assay. Clinical pharmacology studies, using pazopanib 800 mg once daily, have demonstrated that pazopanib does not have a clinically relevant effect on the pharmacokinetics of caffeine (CYP1A2 probe substrate), warfarin (CYP2C9 probe substrate), or omeprazole (CYP2C19 probe substrate) in cancer patients. Pazopanib resulted in an increase of approximately 30% in the mean AUC and C_{max} of midazolam (CYP3A4 probe substrate) and increases of 33% to 64% in the ratio of dextromethorphan to dextrophan concentrations in the urine after oral administration of dextromethorphan (CYP2D6 probe substrate). Co-administration of pazopanib 800 mg once daily and paclitaxel 80 mg/m² (CYP3A4 and CYP2C8 substrate) once weekly resulted in a mean increase of 26% and 31% in paclitaxel AUC and C_{max}, respectively. [See Drug Interactions (7.2).]
Utilization of Cocktail Approach in Assessing Drug Interactions

• Leverage *in vitro* and *in vivo* drug interaction data

• Simultaneously determine the interaction potential on multiple pathways
  – Determine the need for further in vivo studies

• Results from studies may be used to provide guidance for drug administration in product labeling
  – “Cocktail” probe validation (ensure no interaction and robust analytical assays)
  – Sound study design (dose and dosing regimen), sufficient number of subjects, and appropriate sample collection
Utilization of Cocktail Approach in Assessing Drug Interactions (2)

- New cocktails may be developed to include probe substrates for
  - CYP2B6
  - CYP2C8
  - Transporters (e.g., P-gp, OATP1B1, etc)
  - UGT
- Patient genotypes need to be considered for data interpretation or studying gene-drug interaction effect.
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Thank You!

Questions?

leik.zhang@fda.hhs.gov