Are We Getting the Best Return on Investment From Drug-Drug Interaction Studies?

The New England Drug Metabolism Discussion Group
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Outline

1. Incidence and public health impact of DDIs
2. ROI concept applied to DDI studies in NDAs
3. Compare DDI study results from 3 separate years
4. Ideas for complementing current DDI studies
What Is the Incidence and Public Health Impact of DDIs?

- We really don’t know?
- Range from 0.5% to 20% in most studies
  - Ambulatory vs hospital admissions
  - Disease-specific vs general medicine
  - Single drug pairs vs polypharmacy
  - NTI or not
  - Elderly vs younger adults
  - Co-morbidities
  - At-risk extrinsic factors
  - Assumptions about causality
  - Different definitions of a significant DDI
What Is a Significant DDI?

- Significant increase/decrease in mean AUC and/or Cmax ratio of [drug pair/drug alone]
  - p-value, 90% CI 80-125, rule of thumb of 0.5-2.0

- Different 90% CI than 80-125% defined by PK/PD relationship or exposure range in phase 2/3 trials

- Intuitive and additive PD effects (on- or off-target) in absence or presence of significant PK change

- Increased safety risk (rate/severity) with drug pair vs single drug in phase 2/3 trials with/without PK data
## Attempts to Define Level of Severity of DDIs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PK</th>
<th>PD</th>
<th>Clinical</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>No interaction</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Common (71%)</td>
</tr>
<tr>
<td>Clinically unimportant interaction</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Occasional (14%)</td>
</tr>
<tr>
<td>Clinically important interaction</td>
<td>+ or -</td>
<td>+ or -</td>
<td>+</td>
<td>Unusual (14%)</td>
</tr>
<tr>
<td>Hazardous interaction</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>Rare (0.2%)</td>
</tr>
</tbody>
</table>

Conclusion: given the number of possible DDIs, the number of actual serious interactions seems small.

Consensus on Known Risk Factors For Clinically Significant DDIs

- Small molecules
- Older drug pairs
- Orally administered
- Additive PD
- NTI with steep PK/PD curves,
- Large interindividual variability
- Sick and/or elderly patients
- Diseases with multidrug regimens
Two Key Challenges With DDI Studies

- High % of “negative” (no interaction) studies
- Failure to detect serious “positive” or hazardous DDIs
Example of Two Drugs From 2011 Cohort

NMEs Approved for Chronic Hepatitis C

<table>
<thead>
<tr>
<th></th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK DDIs studies</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>NME as Victim</td>
<td>21 (1)*</td>
<td>17 (0)</td>
</tr>
<tr>
<td>NME as Perpetrator</td>
<td>23 (4)</td>
<td>27 (5)</td>
</tr>
</tbody>
</table>

Conclusion: 89% of studies concluded no interaction

* Positive DDI study: 0.5 < AUC ratio > 2.0
Trends in Mean Number of DDIs in NME NDAs

Average Number of DDI Studies per NME

http://www.centerwatch.com/drug-information/fda-approved-drugs/
Retrospective Analysis of the 1996 NME Cohort

- 40% had no *in vitro* metabolism data
- 50% used warfarin, digoxin and cimetidine
- median number of subjects was 12
- 20% used 90% CI for significance
- 21% used pop PK
- 82% of studies concluded no interaction

The Difference Between ROI and Value

**ROI**: amount and type of data or information returned for a given cost of a specific study

**Value**: something created when people engage data or information and are influenced by it to take some action

**Clinical utility**: refers to the translational relevance of information (“actionable”)
“As we all know, drug labels are quite long and involved. Should FDA put information in labels about subgroups whether effects were found or not? Negative studies may be considered non-informing by some but others may want to know that the research was done and nothing was found”

FDA clinical pharmacology advisory committee on DDIs, Sept 25, 2013
FDA public hearing on subgroup data in NDAs. April 1, 2014
Clinician Concern Over Too Much Information on DDIs

• Electronic alerts for positive PK DDIs may generate false alerts (no clinical significance)

• Alert overrides of positive PK DDIs have ranged from 35% to as high as 88%

• Excess alerts desensitize clinicians so that they may ignore fatal alerts of clinical significance

Ahn et al, Pharmacoepi and Drug Safety (2014); 23: 390-397
“…..recruitment of patients from each of the following groups is suggested:”
METHOD

Mean AUC and Cmax arithmetic and geometric ratios (RI/healthy volunteers) were collected (when available) from NDA reviews and drug labels of 277 NMEs approved between 2000 and 2012.
Results

I.R. Younis (FDA), ROI of PK studies in subject with MRI. ASCPT annual meeting poster (2014)
Conclusions

- 95% of studies concluded **no effect on PK in mild RI**
- 4%: dose adjustment and 1%: contraindication.
- Mild RI studies only for NTI drugs and in elderly
- Confirm lack of effects by enrolling patient with mild RI in phase 2/3 studies

Only 3 of 128 NDAs had AUC ratios > 2 in mild RI

I.R. Younis (FDA), ROI of PK studies in subject with MRI. ASCPT annual meeting poster (2014)
Results from in vitro studies (and in silico PBPK modeling) are a screening mechanism to identify the need for in vivo studies.

How many in vivo studies are conducted because of positive in vitro studies?
METHOD

Reviewed 152 cancer drug pairs for PK DDI studies published between 2007-2011. A positive DDI study was one with a statistically significant change in AUC or Cmax.

Results and Conclusions

- 92% (140/152) of studies concluded no interaction (negative)
- 8 of the 12 (75%) positive studies had a mechanistic CYP or transporter rationale
- 19 of 28 (68%) negative studies had a mechanistic CYP or transporter rationale

## Problem of Sensitivity and Specificity of In Vitro Screens

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>67%</td>
<td></td>
<td>30%</td>
<td>69%</td>
</tr>
<tr>
<td>Specificity</td>
<td></td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relatively low false negatives</td>
<td>Relatively high false positives</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Sensitivity:** high, so negative in vitro screen means an in vivo DDI is unlikely.  
**Specificity:** low, so positive in vitro screen is not very helpful.

*False positives (industry burden) >> False negatives (regulatory risk)*
Sensitivity vs Specificity of *In Vitro* Screening
Human Implications of Low Specificity and High Rate of False Positives

Significant investment of time in study design, study conduct, intensive blood draws, sample processing, data analysis, risk of ADRs and may draw away of patients from phase 2/3 trials
Calculations:

- 152 studies
- 24 subjects/study
- 20 plasma samples/subject
- $100/sample
- Total cost of all studies: $7,300,000
- Total cost of negative studies: $5,475,000
- **Cost to detect a single positive study:** $608,000
Caveat: DDIs Are Conducted in the Absence of a Positive or Negative In Vitro Screen

<table>
<thead>
<tr>
<th>Reason(s)</th>
<th>Example of Scenario(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid exclusion criteria for phase 2/3</td>
<td>OC as a victim drug</td>
</tr>
<tr>
<td>Co-administration likely in clinical practice</td>
<td>Statins as a victim drug</td>
</tr>
<tr>
<td>Differentiate product in marketplace</td>
<td>Prasugrel vs clopidogrel</td>
</tr>
<tr>
<td>Mitigate regulatory concerns about safety</td>
<td>Additive QTc prolongation</td>
</tr>
<tr>
<td>Improve benefit/risk ratio</td>
<td>Long-acting insulin + metformin</td>
</tr>
<tr>
<td>Suggested by guidance</td>
<td>Therapeutic protein interactions</td>
</tr>
</tbody>
</table>

Note: neither FDA nor industry has estimated the relative number of DDI studies conducted with or without a mechanistic rationale but that information would be useful to know.
Very Useful to Learn from IVIVE

- No incentive to repeat the studies
- Analysis can improve future *IVIV* extrapolations

<table>
<thead>
<tr>
<th>In vitro test results</th>
<th>Clinical DDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRESENT</td>
</tr>
<tr>
<td>Positive</td>
<td>True positive</td>
</tr>
<tr>
<td>Negative</td>
<td>False negative</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td></td>
<td>False positive</td>
</tr>
<tr>
<td></td>
<td>True negative</td>
</tr>
</tbody>
</table>
Purpose of the UF CPSP DDI Study

1. To determine the rate of positive and negative DDI studies in the 2004, 2012 and 2013 NME cohorts

2. To determine the clinical utility (label recommendations) for positive DDIs for each of the 3 annual cohorts.
### Experimental Design

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2012</th>
<th>2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of drugs</td>
<td>27</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Number of studies</td>
<td>246</td>
<td>155</td>
<td>116</td>
</tr>
</tbody>
</table>

- Data from approved drug labels and drugs@fda
- Information extracted
  - Elimination pathways, $F_m$, PPB etc
  - 90% CI for AUC and $C_{\text{max}}$
  - NME as victim or perpetrator
  - Label recommendations

Limitation: we did not look for any in vitro rationale for conducting clinical DDI studies but did exclude NMEs where DDIs are unlikely
Experimental Design

• **Positive PK DDI study**: geometric mean Cmax and/or AUC ratio of [NME-drug pair / NME alone] did not fall completely within the 90% CI of 80-125%

• **Negative PK DDI study**: geometric mean Cmax and/or AUC ratio of [NME-drug pair / NME alone] was completely within the 90% CI of 80-125%

• **We did not explore the influence of dose, route of administration, study design, use of PBPK, healthy volunteers vs patients or approved indication**
Experimental Design

We defined *clinical utility* only for positive PK DDI studies (i.e., those having a statistically significant increase or decrease in Cmax and/or AUC ratios in terms of actionable information in product label

1. Contraindication
2. Warning and precaution
3. Change in dosing and administration
4. Therapeutic drug monitoring

Note: we did not include the following label language as having clinical utility: “no significant change in Cmax and/or AUC”, “use caution because of increase in exposure” or “start with low dose and titrate upwards”
Results: 2013 Cohort By Therapeutic Area

% refers the distribution of approved NMEs (n= 27) by therapeutic area. There were 25 small and 2 large molecule NMEs in the cohort.
Results: 2013 Cohort – Positive and Negative DDI Studies by Therapeutic Area
Results: 2013 Cohort – Positive and Negative Studies as Victim or Perpetrator

- **Victim**: 25% Significant, 22% Not Significant
- **Perpetrator**: 18% Significant, 35% Not Significant
Results: 2013 Cohort – Positive and Negative DDI Studies for Each Drug

Overall, 112 (46%) of DDIs were positive
## Influence of No Effect Boundaries on Concluding Positive (Significant) t DDI Studies

<table>
<thead>
<tr>
<th>No Effect Boundary Criteria</th>
<th>Significant changes in AUC or Cmax</th>
<th>2013 Cohort (n = 256)</th>
<th>2012 Cohort (n = 155)</th>
<th>2004 Cohort (n = 116)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0.8 to 1.25</strong></td>
<td>Yes</td>
<td>43%</td>
<td>45%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>57%</td>
<td>55%</td>
<td>76%</td>
</tr>
<tr>
<td><strong>0.5 to 2.00</strong></td>
<td>Yes</td>
<td>23%</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>77%</td>
<td>85%</td>
<td>89%</td>
</tr>
</tbody>
</table>
Results: **2013 Cohort** – Label Recommendations of Significant DDI Studies By **Number of NMEs**

Number of NMEs (n=27) with labels influenced by DDI studies

Note: One study for a given NME may appear in 3 different sections of the label
Results: **2013 Cohort** – Distribution of Label Recommendations for Number of DDI Studies

Impact of 256 DDI studies for 27 NMEs

Note: **144 studies (56%)** concluded no interaction. Also, several contraindications were based on additive PD and not PK changes
Results: 2004 Cohort – Clinical Utility of PK DDI Studies By Number of Studies

Impact of 116 DDI studies for 39 NMEs

Note: **88 studies (76%)** concluded no interaction
Comparison of Clinical Utility of Positive DDI Studies Between 2013 and 2004

2013: 253 studies, 144 negative PK change, 112 positive PK change
2004: 116 studies, 88 negative PK change, 28 positive PK change
How to Improve DDI Detection Strategies

In vitro mechanistic screening

Mechanistic systems pharmacology approach

Targeted post-marketing data mining

Less exclusion criteria in phase 2/3 clinical trials

In silico PBPK modeling of positive DDIs

Confirmatory clinical DDI studies

Pop PK in phase 2/3 clinical trials (efficacy & safety)
Pravastatin-paroxetine DDI not found in clinical trials/formal studies
Cohorts: diabetics (n=104) and non-diabetics (n=135); hyperglycemia
Mined FAERS for hypothesis; confirmed in institutional EMRs
Hyperglycemic mechanism confirmed in rodent studies

Mechanistic Systems Pharmacology Approach (MASER®)

✓ Map 2,300,000 case reports in FAERS to molecular knowledge about
✓ 2000 drugs, 500 drug classes, 1100 targets, 900 pathways and 300 CYPs and transporters

✓ Associate ADRs with DDIs at levels of targets, pathways, genes, CYPs and transporters

✓ Look at specific drug pairs, drug classes, specific diseases and link to label recommendations
17.6% of cancer cases are associated with DDIs contraindicated in label.
Summary

1. It is critical to analyze the research that is done in drug development and estimate the ROI, value and clinical utility of results

2. The ROI of DDI studies has increased markedly in terms of more positive and less negative studies from 2004 to 2013

3. There is still much to learn from IVIVE and there is room for improvement in DDI studies
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Thank You For Your Time and Attention

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