Clinical Pharmacology 2: Clinical Pharmacology Considerations During Phase 2 and Phase 3 of Drug Development

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Objectives

• Describe information needed to interpret clinical significance of factors that alter drug exposure
• Discuss the need to evaluate specific populations
• Discuss Phase 2 and Phase 3 drug development decisions that are affected by drug interaction information
• Understand the impact of complete and incomplete clinical pharmacology programs on information available to health care providers
Outline

- The goals of a clinical pharmacology program throughout drug development
- The value of exposure-response information
  - specific situations when the information is valuable
- Barriers to informative exposure-response evaluation
- Case studies (drug interactions)
- Conclusions- relevance and impact
The Ultimate Goal

- Right Drug
- Right Patient
- Right Dose
- Right Time

FDA
Phases 2 & 3 of Drug Development

Phase 2 studies

- provide preliminary data on the effectiveness of the drug
- allow selection of appropriate dose range for evaluation in Phase 3

Phase 3 studies

- provide pivotal information about effectiveness and safety
- allow evaluation of the overall benefit-risk relationship of the drug
Exposure-response relationship

- Determine relationships for safety and efficacy in phase 2 and phase 3

Exposure (drug concentration, AUC, Cmax, Cmin)

Response

Efficacy

Toxicity

Level of acceptable toxicity
The value of exposure-response information
Add to weight of evidence supporting efficacy and safety

- Allow better understanding of clinical trial data
- Explain results based on concentration data and knowledge of exposure-response relationship
  - Resolve safety concerns
  - Understand or support evidence of subgroup differences
New drug administration scenarios

- New dosing regimen (e.g., BID to QD)
- New dosage form or formulation
- New route of administration
New Dosing Regimen

![Graph showing concentration over time for Test QD and Reference BID dosage regimens.](image)
New Formulations
New Populations or Specific Populations

EXAMPLES-

• Age groups
  – Elderly
  – Pediatric (decision tree)

• Renal or Hepatic Impairment
  – consider phase 1 results
  – can collect exposure data in Phases 2 and 3

• Women

• May not be possible to adjust the dose to achieve similar AUC, Cmax and Cmin as in previous population
Pediatric Study Decision Tree

Reasonable to assume (pediatrics vs adults)
-- similar disease progression?
-- similar response to intervention?

NO
-- Conduct PK studies
-- Conduct safety/efficacy trials

NO
Is there a PD measurement that can be used to predict efficacy?

YES
Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?

YES TO BOTH
-- Conduct PK/PD studies to get C-R for PD measurement
-- Conduct PK studies to achieve target conc. based on C-R
-- Conduct safety trials

NO
-- Conduct PK studies to achieve levels similar to adults
-- Conduct safety trials
Bioequivalence (BE) Studies

• (Pivotal BE) Formulation change after phase 3 studies are complete
• Alter formulation of active control (blinding)

• For valid phase 3 results
  – need to determine whether the formulation change alters exposure
  – if exposure changes, are the changes clinically relevant?
Bioequivalence

- Concentration (mcg/mL) vs. Time (hours)
  - Reference
  - Test 1
  - Test 2
Impact of food effect

- Administration of drugs with food may....
  - Alter drug concentrations (increase or decrease)
  - Alter efficacy and safety
- A possible scenario.....

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Efficacy</td>
</tr>
<tr>
<td></td>
<td>Fed patients</td>
</tr>
<tr>
<td></td>
<td>Most patients</td>
</tr>
<tr>
<td></td>
<td>Toxicity</td>
</tr>
</tbody>
</table>

Level of acceptable toxicity
Impact of food effect
Possible sequence of events...

• First food effect study: no effect of food
• Phase 2 studies allow administration with or without food; evaluate a range of doses
• Formulation change prior to Phase 3
  – New formulation is not bioequivalent to old formulation, but it is possible to select a dose for Phase 3
• New formulation is administered without food restrictions in Phase 3
Impact of food effect
Possible sequence of events...

- Food effect study conducted in parallel with Phase 3 trials
  - Food decreases AUC and Cmax by 30%

- The results of the Phase 3 study (conducted with no food restrictions) are positive: the drug is safe and effective
  - Can we conclude that the food effect is not clinically significant?
Impact of food effect
Possible sequence of events...

• ..... Can we conclude that the food effect is not clinically significant?

• To answer the question, consider-
  – How often was drug given with food/without food
  – Exposure-response relationship
Barriers to informative exposure-response evaluation
Barriers to informative exposure-response evaluation

- Exposure data are not collected in late phase 2 or phase 3
- Study design flaws
- Study conduct flaws
Study Design Flaws

• Under-powered for study objectives
• Doses
  – too few
  – doses too close together
• Plasma samples
  – inappropriate timing
  – insufficient number
  – sample for only one drug in multidrug therapy
**Flaws in Conduct of Study**

- **Poor record-keeping**
  - dosing times
  - plasma sample times

- **Analytical methods**
  - bioanalytical method for PK unacceptable
Two case studies
Case 1 - Maraviroc

- HIV CCR5 inhibitor
- Indication: treatment of HIV infection in patients infected with CCR5-tropic HIV-1 virus
**Maraviroc**

**Phase 2b/3 Dose Selection**

- **Phase 2a conclusion (Viral dynamic modeling; exposure-response evaluation)**
  - Evaluate maraviroc 300 mg qd and 300 mg bid in Phase 2b/3

- **Drug interaction data**
  - Maraviroc is a CYP3A substrate
  - Other drugs in antiretroviral regimen may increase or decrease maraviroc concentrations
  - Maraviroc does not affect concentrations of other drugs
Maraviroc
Phase 2b/3 Dose Selection

Drug interaction results

- **Effect of other drugs on maraviroc**
  - CYP3A inhibitors- $\uparrow$maraviroc concentrations 3-11 x
  - CYP3A inducer (efavirenz)- $\downarrow$maraviroc concentrations by 50%
  - CYP3A inducer (nevirapine)- little effect on maraviroc concentrations
  - CYP3A inhibitor and inducer- $\uparrow$maraviroc concentrations
## Maraviroc Phase 2b/3 Doses

Doses were selected based on exposure-response information and drug interaction study results.

<table>
<thead>
<tr>
<th>Concomitant medications</th>
<th>Maraviroc Phase 2/3 dose (q.d or b.i.d.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP3A inhibitor</strong> (with or without CYP3A inducer), including Protease inhibitor (except tipranavir/rtv)</td>
<td>150 mg</td>
</tr>
<tr>
<td><strong>CYP3A inducers</strong> (efavirenz)</td>
<td>600 mg</td>
</tr>
<tr>
<td><strong>Other concomitant medications</strong></td>
<td>300 mg</td>
</tr>
</tbody>
</table>
Case 2 - Etravirine

• Non-nucleoside reverse transcriptase inhibitor for treatment of HIV (part of combination therapy)

• Two identical phase 3 studies
  – Etravirine 200 mg b.i.d. + optimized therapy that included darunavir/ritonavir 600/100 mg b.i.d.
  – Vs. optimized therapy that included darunavir/ritonavir 600/100 mg b.i.d.
Drug interaction: etravirine and darunavir/ritonavir

- Phase 1 drug interaction study results
  - coadministration of darunavir/ritonavir decreases etravirine plasma concentrations by 30 to 50%

- No efficacy concern - the etravirine efficacy data were collected in the presence of darunavir/ritonavir
Potential safety concern

- Etravirine may be administered without darunavir/ritonavir.
- Etravirine may be administered with drugs that increase its concentrations.
- Thus, etravirine plasma concentrations may be higher than observed in Phase 3 studies.
  - How much higher?
  - Are the higher concentrations safe?
  - What is the risk/benefit for specific populations?
Etravirine + lopinavir/ritonavir (How much higher?)

- ↑ mean etravirine AUC by 17%
- (↑ mean etravirine AUC by ~85% compared to etravirine + darunavir/ritonavir)
- No effect on lopinavir concentrations
### Etravirine + Lopinavir/Ritonavir
Are higher concentrations safe?

<table>
<thead>
<tr>
<th>AUC12 (ng*hr/mL) range</th>
<th>Observation from Phase 3 data</th>
<th>Multiply each AUC by 1.85 to account for administration of lopinavir/rtv rather than darunavir/rtv</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>145 to 69,997</td>
<td>268 to 129,495</td>
</tr>
<tr>
<td>% subjects with AUC &gt; 70,000</td>
<td>0</td>
<td>0.51%</td>
</tr>
<tr>
<td>% subjects with AUC 50,000 to 70,000</td>
<td>0.34%</td>
<td>0.51%</td>
</tr>
<tr>
<td>% subjects with AUC 30,000 to 50,000</td>
<td>0.69%</td>
<td>4.47%</td>
</tr>
<tr>
<td>% subjects with AUC 10,000 to 30,000</td>
<td>16.67%</td>
<td>48.97%</td>
</tr>
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</table>
Etravirine + Lopinavir/Ritonavir Risk/benefit

Considerations

- etravirine concentration data from Phase 3
- anticipated etravirine concentrations when etravirine is given with LPV/RTV
- the population that would receive lopinavir/ritonavir instead of darunavir/ritonavir
- safety risks of etravirine
Conclusions: Relevance and impact
If a tree falls in the forest and no one hears it, does it make a sound?
If an exposure-response relationship exists for a drug, but drug concentrations are not determined during phase 2 or phase 3, can we optimize therapy for all patient populations?
Answer: NO!!

Other versions of the answer:
• You don’t know what you don’t know
• Ignorance is not bliss
Conclusions (relevance and impact)

• Without exposure-response information
  – Dose selection may not be optimal
  – We cannot interpret significance of exposure changes

• Result: Lack of dosing instructions for certain groups
  – They are deprived of therapy
  – Or, they risk suboptimal safety and efficacy