Regulatory and Scientific Challenges for Drug-Drug Interactions

Shiew-Mei Huang  
Lei Zhang  
Office of Clinical Pharmacology, OTS, CDER, FDA

Drug Interactions - One Survey -

- National survey of 3005 community-residing older adults (>57 YO) in US
- 80% of individuals takes ≥ 1 medical product (prescription, OTC, supplement)
- 50% takes at least 5 medical products
- 30% takes at least 5 prescription drugs  
→ 1/25 at risk of major drug-drug interactions


- Do we need an updated list such as this one? (“Drug Interaction Checks” enabled as part of the EHR implementation- HealthIT.Gov)
- Which databases? (e.g., the above used micromedex)
- When are we concerned about complex interactions (multiple drugs)?  
→ Critical in the mechanistic understanding of these PD- and PK-based interactions and the ability to extrapolate to untested conditions

Many Factors Affect Drug Exposure/Response

It is critical to evaluate how these factors affect drug exposure/response  
Ultimate goal → Optimal dosing for patients with these individual factors

Impact of Intrinsic Factors

- What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and
- What is the impact of any differences in exposure on efficacy or safety responses?

Dose Adjustment (1)

Impact of Intrinsic Factors

Dose adjusted from the population dose(s) for individual groups of patients with specific intrinsic factors

Impact of Extrinsic Factors

- What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response?
- What is the impact of any differences in exposure on response?

Dose Adjustment (2)

Impact of Extrinsic Factors

Dose adjusted from the population dose(s) for individual groups of patients with specific extrinsic factors


Impact of Intrinsic Factors


Impact of Extrusive Factors

Application of Pharmacogenomics in Drug Development, Regulatory Review and Clinical Practice
UCSF-Stanford CERSI, September 23, 2015, Stanford, CA
Increasing Information on Transporter

Red: Critical transporter proteins to evaluate prospectively
Green: Additional ones to evaluate prospectively
Yellow: Retrospective evaluation
Blue: Additional transporters


Simeprevir & P-gp

In vitro, simeprevir is a substrate for P-gp, MRP2, BCRP. OATP1B1 and OATP2B1; simeprevir inhibits the uptake transporters OATP1B1 and NTCP and the efflux transporters P-gp/MDR1, MRP2 and BSEP. The inhibitory effects of simeprevir on the bilirubin transporters OATP1B1 and MRP2 likely contribute to clinical observations of elevated bilirubin (see Adverse Reactions (6.1)).

7 DRUG INTERACTIONS
7.1 Potential for OLYSIO to Affect Other Drugs
7.2 Potential for Other Drugs to Affect OLYSIO
7.3 Established and Other Potentially Significant Drug Interactions

Dilganim
† digoxin

Concomitant use of OLYSIO with digoxin resulted in increased plasma concentrations of digoxin due to inhibition of P-gp by simeprevir. Routine therapeutic drug monitoring of digoxin concentrations is acceptable.

Drugs at the FDA (OLYSIO): 7.3 Drug Interactions: 2015 Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205123s008lbl.pdf

Simeprevir & OATP1B1

In vitro, simeprevir is a substrate for P-gp, MRP2, BCRP. OATP1B1 and OATP2B1; simeprevir inhibits the uptake transporters OATP1B1 and NTCP and the efflux transporters P-gp/MDR1, MRP2 and BSEP. The inhibitory effects of simeprevir on the bilirubin transporters OATP1B1 and MRP2 likely contribute to clinical observations of elevated bilirubin (see Adverse Reactions (6.1)).

Drug: CO-A Reductase Inhibitors

Rosuvastatin
† rosuvastatin

Concomitant use of OLYSIO with rosuvastatin resulted in increased plasma concentrations of rosuvastatin due to inhibition of OATP1B1 by simeprevir. Initiate rosuvastatin therapy with 1 mg once daily. The rosuvastatin dose should NOT exceed 20 mg daily when co-administered with OLYSIO.

Drugs at the FDA (OLYSIO): 12.2 Clinical Pharmacology & 7.3 Drug Interactions: 2015 Labeling
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205123s008lbl.pdf

Regulatory Guidance/Guideline on Drug Interactions


- European Medicines Agency (EMA) Guideline on the Investigation of Drug Interactions (effective Jan 2013)

- Pharmaceuticals Medical Devices Agency (PMDA) Draft Guideline on Drug Interactions (2013)
  http://search.e‐gov.go.jp/servlet/Public?CLASSNAME=PCMMSTDETAIL&id=495130206

Mechanisms of Drug Interactions

Pharmaceutical
Dosage form interactions
Pharmacokinetic
Alterations in
Absorption, Distribution, Metabolism, Excretion

Transporters
Phase I enzymes
Phase II enzymes

Pharmacodynamic

Shiew-Mei Huang
Application of Pharmacogenomics in Drug Development, Regulatory Review and Clinical Practice
UCSF-Stanford CERSI, September 23, 2015, Stanford, CA
### Major PK Drug Interactions Mechanisms

**Inhibition or Induction of Metabolizing Enzymes and/or Transporters**

- **Drug 1 (Parent)**
  - **Induction** → ↑
  - **Inhibition** → ↓

**Exposure**
- **AUC or Cmax**
  - Induction:
    - **Concern**
    - **Efficacy**
  - Inhibition:
    - **Concern**
    - **Safety**

**AUC**: Area under the curve
**Cmax**: Maximum plasma concentration

---

### Drugs are metabolized by a variety of enzymes

- Approximately 70% of all drug metabolism in humans is mediated by CYP (or P450) enzymes (Phase I enzymes)
- Of the more than 50 CYP enzymes
  - CYP (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4) account for >95% of xenobiotic metabolism
  - CYP3A is the major CYP, ~50% of drugs were metabolized by CYP3A

### Clinical implications of inhibition and induction of drug metabolizing enzymes or transporters

- **Perpetrator (Inhibitor or Inducer)**
  - **Drug 2**
  - **Drug 1**
  - **Metabolizing enzyme or transporter**

**Exposure**
- **AUC or Cmax**
  - Induction:
    - **Concern**: Efficacy
  - Inhibition:
    - **Concern**: Safety

### Transporters

- Transporters are transmembrane proteins that are inserted in cell membranes to translocate substances across the membrane
- More than 400 transporters are identified:
  - ~30 contribute to the efficacy and safety of drugs
  - Two super families:
    - **ABC Transporters (~50 families)** (ATP-binding cassette)
      - e.g., P-glycoprotein (P-gp, MDR1)
    - **SLC Transporters (~350 families)** (Organic Solute Carrier Transporters)
      - e.g., Organic anion transporting polypeptides (OATPs)

### Transporters of Clinical Importance

- Red: Critical transporter proteins to evaluate prospectively
- Yellow: Additional one to evaluate prospectively
- Green: Retrospective evaluation

### Drug Interaction Potential Evaluation

**Other drug’s effect on NME**:
- Whether an NME is a substrate for
  - CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A
  - P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3
  - MATEs

**NME’s effect on other drug**:
- Whether an NME is an inhibitor for
  - CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A and P-gp
  - P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3
  - MATEs

- Whether an NME is an inducer for
  - CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A
  - P-gp (evaluate with CYP3A)
**In vitro metabolism results: Is NME a substrate?**

- P450 (CYP) substrate
  - CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A1

- Pathway major?
  - No
  - Yes

- In vivo: most potent inhibitor/inducer. Is interaction significant?
  - No further in vivo studies needed
  - Yes

- Does NME affect the drug level?
  - Yes
  - No

- Is the drug affected by NME?
  - Yes
  - No

*Evaluation of non-CYP enzymes may be important in some cases.*

---

**In vitro metabolism results: Is NME an inhibitor or inducer?**

- P450 inhibitor or inducer
  - CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A1

- Stop: No in vivo study
  - Yes
  - No

- In vivo study: sensitive substrate. Is there a significant interaction?
  - No
  - Yes

- Consider the need for more in vivo studies or mechanistic modeling assessment:
  1. Magnitude of interaction
  2. Risk vs. benefit (exposure-response)
  3. Other drug interaction information needed for safe administration of drug?

---

**NME as a Substrate**

**Does the drug level depend on a given transporter?**

- Route of elimination
  - Hepatic major
  - Renal major
  - Rate limiting step

- Physicochemical properties of the drug
  - e.g., BCS or BBDCS

- Structure
  - e.g., OAs for anions and OCTs for cations
  - Caveat: some cations transported by OATs (cimetidine, sitagliptin)

- Similarity to known substrates

- In vitro assays → A mechanistic understanding of the clearance of the drug
  - Sources of variability and potential for DDI

- Other factors to consider for DDI studies:
  - Safety margins, therapeutic range, co-medications that are known transporter inhibitors in the indicated patient populations, is there known polymorphism of the transport pathway?

---

**NME as an Inhibitor**

**Does the drug affect a given transporter?**

- Inhibitors can be substrates or non-substrates for a given transporter.

- The need to study DDI depends on whether drugs are likely co-administered with known substrates of major human transporters.

- Other factors to consider: indications, and whether the NME may affect other pathways.
Evaluation of NME as an Inhibitor for Transporters

Does the drug affect a given transporter?

**Goal:** Determine whether in vivo studies are needed based on in vitro assessment. It is not intended to use in vitro data to determine the magnitude of an in vivo interaction.

---

**Criteria:**
- Relevant inhibitor concentrations/in vitro IC_{50} > cutoff value?
- In vivo interaction potential

**P-gp, BCRP:** Gut concentration (Dose/250 mL)

**OATP1B:** Free inlet concentration

**OAT1/OCT2/MATEs:** Free systemic concentration

---

### In Vitro Methodologies

- **In vitro assessments** are critical to help determine the clearance mechanism and DDI potential.
- "Best Practice" of in vitro assay methodology is needed to ensure quality of in vitro assessments (e.g., reliable, reproducible and validated).
- The sources of the variability need to be understood, e.g.,
  - Different laboratories
  - Different in vitro cell systems
  - Different substrate/inhibitor
- The processes need to be standardized in each laboratory.
  - Each laboratory may develop criteria internally with known positive and negative controls ("calibration")

Need best practices and standardized approaches

---

### Recommendations related to transporters

- **Recommended sponsors** to evaluate major transporters as described in the ITC paper
- Continuing dialog with industry, academia, other regulatory agencies
- Consulting and collaborating with experts in the field (ITC, IQC and academia, CYP inhibition and induction workgroups as an example; sabbatical scientists)
- FDA OCP Transporter Scientific Interest Group continuing research to refine/refine in vitro criteria in determining the need to conduct in vivo studies

---

### Challenges and Gaps between In Vitro and In Vivo

**P-gp (using [I]_{in} or [I]_{out}/[C]_{sub})**
- Tramadol / Narlone: False positive -> Concomitant induction?
- Talsirol / Digoxin: False negative prediction

**OATP1B (using Free [I]_{in}/[C]_{sub}, R)**
- Gemfibrozil / Pitavastatin: False negative
- Gemfibrozil glucuronide also inhibits OATP1B
- Teriflunomide / Rosuvastatin: False negative if only consider OATP1B.
- -> BCRP inhibition also involved.

**OCT2** (using Free [C]_{out}/[C]_{sub})
- Dulaglutide / Metformin: False negative using one IC_{50} reported (~20 fold difference from two sources) -> non-specific binding?

**Considerations:**
- Substrate dependent inhibition
- Uncertainty about intracellular concentrations
- Non-specific binding
- Multiple processes
  - (absorption/distribution/excretion)
- Multiple transporters involved
  - Transports-Enzymes Interplay
  - Metabolite as inhibitor
  - Mechanistic discrepancy

---

### FDA Model-Based Framework

- **Mechanistic consideration of individual pathways**

**Investigational Drug as a Perpetrator (Inhibitor or Inducer)**

**Basic**

**Mechanistic, static**

**Mechanistic, dynamic (including PBPK)**

Need to consider all mechanisms (enzyme and transporter) to understand the clearance pathway and to be able to describe PK (and PD) variability

---

Application of Pharmacogenomics in Drug Development, Regulatory Review and Clinical Practice

UCSF-Stanford CERSI, September 23, 2015, Stanford, CA
Complexity of Transporter DDI

- Associated with both drug ADME and DDI potential
  - PK of substrate and interacting drug
  - DDI mechanism(s) of interacting drug
- At all levels of physiology
  - Organ/tissue level (≥ 1 transporter, in ≥ 1 organ)
  - Cell level (differential expression, uptake and efflux, ≥ 1 cell type)
  - Subcellular system
- Enzyme-transporter-(permeability) interplay

Need knowledge integration and mechanistic modeling of local as well as whole body kinetic events

Zhao P, AAPS 2012

Physiologically-based Pharmacokinetics Modeling (PBPK)

Drug Development...
Progressive Reduction of Uncertainty

Janet Woodcock, M.D. CDER Director
FDA PBPK Workshop, March 2014

http://www.fda.gov/drugs/newsevents/ucm387698.htm

Regulatory Submissions with PBPK Data

- Increased use of PBPK by drug developers
- Majority of the cases were related to DDI (~60%)

PBPK & Drug Interactions
Example: Ibrutinib

PBPK-Simulated and observed Cmax and AUC ratios (mean and 95% confidence interval)

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205552Orig1s000ClinPharmR.pdf

Application of Pharmacogenomics in Drug Development, Regulatory Review and Clinical Practice
UCSF-Stanford CERSI, September 23, 2015, Stanford, CA
Ibrutinib Labeling

Section 12.3: "Simulations...suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition;...a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib up to 3-fold.’

Section 2.4: "...strong CYP3A inhibitors which would be taken chronically...is not recommended. For short-term use (treatment for 7 days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics) consider interrupting IMBRUVICA therapy until the CYP3A inhibitor is no longer needed. Reduce IMBRUVICA dose to 140 mg if a moderate CYP3A inhibitor must be used...Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.'

And more in Section 7...

Ibrutinib Labeling

DOSAGE AND ADMINISTRATION

Drug Interactions

Patients taking concomitant strong or moderate CYP3A inhibitors should be monitored more closely for signs of IMBRUVICA toxicity.

Confidence, Limitation and Challenges of PBPK in DDI Prediction

Summary

- Drug interactions is one critical factor in determining the best drug or dose for individual patients
- Recent development of molecular biology has improved understanding of the mechanisms behind drug-drug, drug-juice, drug- supplement interactions
- Careful evaluation of drug interaction potential during drug development provides key labeling information for patients
- FDA and other regulatory agencies have provided guidance on the evaluation of drug interactions
- Continual collaborations among stake holders are key to useful information for patients

References

FDA Drug Development and Drug Interactions Website:
Genomics at the FDA:
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm
Drugs@FDA:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
Clinical Pharmacology Guidance for Industry:
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm
For Consumers:
http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm212747.htm