Clinical Pharmacology: Concepts to Support Drug Development

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Disclaimer

• The opinions contained in this presentation are my own and do not necessarily represent the views of the FDA.
Objectives

- Defining clinical pharmacology
- Clinical pharmacology studies:
  - Timing
  - Goals
  - Key design elements
  - Information gained from these studies
- Learn about typical clinical pharmacology properties that are characterized for a drug
- Labeling examples of the impact of clinical pharmacology studies
How do Clinical Pharmacologists Contribute to the Drug Development Process?

We “own the dose”

– Help determine the dosing regimen of a drug
  • How much to give?
  • How often to give it?

– Help determine if the dose of a drug needs to be adjusted due to various intrinsic/extrinsic factors

Right patient?
Right drug?
Right dose?
Right time?
Clinical Pharmacology—What is it?

• Study of the Pharmacokinetics (PK) and Pharmacodynamics (PD) of a drug in humans

**PK**: what the body does to the drug
(Absorption, Distribution, Metabolism, Excretion)

**PD**: what the drug does to the body

Commonly referred to as an exposure-response (ER) profile
PK and Drug Effect

- **Cmax**: Maximum drug concentration
- **AUC**: Area under the curve
- **Tmax**: Time to maximum drug concentration (Peak effect)
- **Cmin**: Minimum drug concentration (onset of effect)
- **Duration of action**: Time from Tmax to Cmin
- **Therapeutic Window**: Range between Minimum Effective Concentration and Minimum Toxic Concentration
Clinical Pharmacology Studies
Early phase studies are designed mainly to investigate the safety/tolerability (if possible, identify MTD) and pharmacokinetics of an investigational drug in humans.
First-in-Human Study

Starting dose determined by preclinical tox studies

Typically the first-in-human study (or studies)

Randomized, placebo-controlled, healthy volunteers (or patients, in certain cases)

Information gained:

- Safety/tolerability, identify maximum tolerated dose
- General PK characteristics, variability, linearity, dose proportionality
- Steady-state parameters
- Preliminary exploration of drug elimination
ADME (Absorption, Distribution, Metabolism, Excretion) Study

Objective: To understand the full clearance mechanisms of the drug and its metabolites in humans

Information gained:
- Primary mechanism(s) of metabolism and excretion from the body
- Proportion of parent drug converted to metabolite(s)
Bioavailability (BA) Studies

• Objective: To evaluate the rate (Cmax, Tmax) and extent (AUC) of absorption of drug from a test formulation (vs. reference formulation)

• Typically crossover, single dose study in healthy subjects; measure extent and rate of absorption of parent drug and major active metabolites (if any)
  • Can assess relative (one formulation vs. another) or absolute (vs. IV formulation) bioavailability

Information gained:
- Comparison of amount of drug that reaches systemic circulation from each tested formulation
Food Effect Study

Objective: To evaluate the effect of food on rate and extent of drug absorption from a given formulation

- Single dose study in healthy subjects using highest strength of drug product\(^1\).
- Fed state should be FDA high-fat high-calorie meal (other meals can also be studied)
- PK assessments similar to BA study
- No food effect if 90% CI of fed/fasted Cmax and AUC ratios within 80-125%.
- The clinical significance of any observed food effect would be determined based on drug’s exposure-response profile.

Information gained:
- How to administer drug in clinical trials
- Labeling instructions on how to administer drug with respect to food

Hepatic Impairment Study
Decision Tree

Investigational Agent

Chronic, Systemic Drug,
Use Likely in Hepatically impaired

>20% of absorbed drug eliminated by liver
(wide TI); <20% if Narrow TI drug;
% eliminated by liver unknown

Study Recommended

Full Study
(Normal vs. Child-Pugh A, B, C)

Population PK
(if patients included in Ph 2/3 trials)

Single-Use, Inhalational
<20% absorbed drug eliminated by liver
(wide TI drug); eliminated entirely by kidneys

No Study Recommended

Label Accordingly

Reduced Study
(Normal vs. Child Pugh B)

Positive Results for Child-Pugh B:
Dose Reduction;
Use with caution in Child-Pugh-C

Negative Results for Child-Pugh B:
No dosage Adjustment for Child-Pugh A & B

Hepatic Impairment Study

- **Study Designs:**
  - **Full study design:** Single dose, parallel groups, males & females with varying degrees of hepatic impairment (≥6 per group)
    - Normal Hepatic Function (matched for age, sex, & BW to subjects with hepatic impairment)
    - Child-Pugh Class A (Mild)
    - Child-Pugh Class B (Moderate)
    - Child-Pugh Class C (Severe)
  - **Reduced study design:** Normal vs. Child-Pugh B (Moderate) (≥8 per group)
  - **Pop-PK approach (pre-planned analysis):**
    - Should include patients w/ varying degrees of hepatic impairment in phase 2 and 3 trials
    - Should include appropriate evaluation of severity of liver disease

**Information gained:**
- Effect of hepatic impairment on PK of parent drug and metabolites
- Dosage recommendations for various stages of hepatic impairment
Renal Impairment Study
Decision Tree

Investigational Drug

Chronically administered oral, iv, sc and likely to be administered to target population

- Study recommended

Non-renewal predominates

- Reduced PK study (in ESRD patients)¹
  - Negative results
    - Label as such - No dose adjustment
  - Positive results²
    - Label with dose adjustments

Renal clearance predominates²

- Full PK study³
  - Negative results
    - Label as such - No dose adjustment
  - Positive results⁴

Single-dose use Volatile Inhalation
Unlikely to be used in renal impaired patients

- No study recommended
- Label

Source: Renal Impairment Guidance (2010):

¹ Metabolites (active/toxic) follow the same decision tree.
² The sponsor has the option of conducting a reduced study in ESRD patients or a full study.
³ To be conducted in ESRD patients not yet on dialysis.
⁴ The results are "positive" when the PK changes are clinically significant based on exposure-response of the drug.
⁵ See section IV.B for the full PK study design, or additional studies can be conducted including a population PK evaluation.
Renal Impairment Study

- **Study designs:**
- **Full study design:**
  - Generally single dose, parallel groups, “healthy” males and females with varying degrees of renal function (≥6 per group, based on CrCl):
    - Normal (≥90 mL/min)
    - Mild (60-89 mL/min)
    - Moderate (30-59 mL/min)
    - Severe (15-29 mL/min)
    - ESRD (<15 mL/min) dialysis and non-dialysis
- **Reduced study design:**
  - Same general design as full, except only study severes and normals
  - **Pop-PK approach**
  - Include appropriate number of subjects in each impairment group

**Information gained:**
- Effect of renal impairment on drug clearance; dosage recommendations for various stages of renal impairment
- Effect of hemodialysis (HD) on drug exposure; info on whether dialysis could be used as treatment for drug overdosage
Drug Interaction Studies

Use in vitro tests to determine if drug is a substrate for or an inhibitor/inducer of common drug metabolizing enzymes and transporters (e.g., CYP3A, CYP2C9, P-gp, etc)

Conduct drug interaction studies to confirm involvement of drug

Implications for labeling range from informative wording (i.e., drug X is not a substrate for CYP3A-mediated metabolism) all the way to a contraindication

Additional detailed information can be found in the Guidance for Industry: Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications (2017)
Drug Interaction Studies

Some key points to consider:

- Several factors should be taken into account to maximize the possibility of detecting an interaction (and also be clinically relevant):
  - Dose of inhibitor/inducer
  - Route(s) of administration
  - Timing of co-administration
  - Number of doses
- Degree of effect (inhibition/induction) is typically classified by change in the substrate AUC:
  - e.g., Drug causes ≥ 5-fold increase in midazolam AUC → “potent” inhibitor of CYP3A4
- Exposure-response information on the drug is important in assessing the clinical significance of the change in AUC of substrate by inhibitor/inducer.
Timing of Early and Clinical Pharmacology Studies

Pre-Clinical
- Assay Dev't & Validation including stability
- Blood/Plasma ratio; Protein Binding

Clinical
- Phase 1
  - SAD/MAD PK*
  - Food-effect

- Phase 2
  - PK & PD in patients
  - Exposure-Response Analyses

- Phase 3
  - "Pivotal" Bioequivalence

- Phase 4
  - PK in Peds, Geriatrics, Pregnancy/Lactation
  - PK in Renal Impairment
  - PK in Hepatic Impairment
  - Assessment of potential for QT prolongation

In vitro metabolism/transport:
- substrate/inhibition/induction

In vivo DDI studies
- PGx: CYP genotyping
- PGx: Biomarkers of Response

Mass Balance
What do we need to know?
Clinical Pharmacology Properties of a Drug

- **ABSORPTION:**
  - What is the bioavailability and PK variability?
  - Does it exhibit linear PK (e.g. dose-proportional increases in Cmax & AUC) or accumulate over time?
    - Will impact the design of some studies
  - Is exposure significantly affected by concomitant food, pH-altering medications, grapefruit, alcohol, etc?
  - Is absorption affected by transporters?
Clinical Pharmacology Properties of a Drug

• DISTRIBUTION:
  • Does drug reach the target site(s) of action immediately and at effective/nontoxic concentration? Does it accumulate in non-target organs?
  • Does it bind to plasma proteins? Is the extent of protein binding concentration- or time-dependent?
    • only free or unbound drug is active
    • PK in terms of total drug concentrations often sufficient (e.g., in PK studies in renal and hepatic impairment)
  • CSF and others
Clinical Pharmacology Properties of a Drug

• METABOLISM/EXCRETION:
  • Is it metabolized by a CYP or other enzyme?
  • Is CL variable and dependent on ‘covariates’ such as age, race, gender, disease/comorbidities?
  • Is CL time-dependent (e.g., metabolic auto-induction, diurnal variation)?
    • May affect duration or timing of studies for PK profiling
Clinical Pharmacology Properties of a Drug

• OTHERS:
  • A Narrow Therapeutic Index Drug?
    • If yes, slight changes in drug exposure may significantly impact efficacy/safety
    • May require therapeutic drug monitoring in clinical trials and clinical practice to minimize toxicities and lack of efficacy
  • A significant inhibitor or inducer of CYP enzymes or transporters?
    • If yes, further drug interaction evaluation may be needed
Important Exposure Parameters of a Drug

Parent Drug and Active Metabolites:

• $T_{\text{max}}$
  - represents the most appropriate time(s) to perform safety assessments (e.g., vital signs, ECG, other immediate PD effects)

• $t_{\frac{1}{2}}$
  - considered when determining dosage interval
  - related to time to steady state ($t_{ss}$) after dose initiation or dose adjustment; considered in evaluating need for a loading dose
  - influences the duration of monitoring after dosing and follow-up after withdrawal of therapy
  - determines adequate washout period between treatments (in crossover studies)

• $C_{\text{max}}$, $C_{\text{min}}$, $AUC$
  - important for dose selection (eg. PK/PD parameters predicting efficacy of anti-infective drugs)
Clinical Pharmacology Guidance Documents

• General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (2014)
• Clinical Drug Interaction Studies (2017)
• In vitro Drug Interaction Studies (2017)
• Clinical Pharmacogenomics (2011)
• Clinical Lactation Studies (2005)
• Pharmacokinetics in Patients with Impaired Hepatic Function (2003)
• Pharmacokinetics in Patients with Impaired Renal Function (2010)
• Pharmacokinetics in Pregnancy (2004)
• Population Pharmacokinetics (1999)

Site: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm
Biopharmaceutics Guidance Documents

- Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (2015)
- Bioanalytical Method Validation (2013)
- Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations (2014)
- Statistical Approaches to Establishing Bioequivalence (2001)

Site: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm
The impact on labeling
Phase 1 Studies: Impact on Labeling

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
  8.1 Pregnancy
  8.2 Labor and Delivery
  8.3 Nursing Mothers
  8.4 Pediatric Use
  8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
  9.1 Controlled Substance
  9.2 Abuse
  9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
  12.1 Mechanism of Action
  12.2 Pharmacodynamics
  12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
  13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
  13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
Food Effect Example:
REYATAZ® (atazanavir) oral capsules

- Administration of a single dose of atazanavir (800 mg) with a light meal increased Cmax by 57% and AUC by 70%; a high-fat meal increased AUC by 35% with no change in Cmax. The %CVs of AUC and Cmax decreased by approximately one-half compared to the fasting state.

- Clinical trials were conducted under fed conditions.

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021567s039,206352s004lbl.pdf

Label directs administration with food.
In an ADME study, ~93% of the dose was excreted in urine by 12 hours.

Because doripenem is primarily eliminated by the kidneys, a full PK study in patients with renal impairment was conducted. The study demonstrated a significant difference in PK between patients with moderate and severe renal impairment compared to those with normal renal function. Also, 52% of the dose was recovered in the dialysate following dialysis.

In Phase 2/3 trials, dosage was adjusted based on CrCL.

The label recommends dosage reduction for patients with moderate or severe renal impairment... and hemodialysis as a treatment for overdosage.

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022106s015lbl.pdf
Hepatic Impairment Example: ISENTRESS® (raltegravir) oral tablets

• A mass balance study showed that raltegravir is eliminated primarily by glucuronidation in the liver. Renal clearance is a minor pathway of elimination.

• In the hepatic impairment study (reduced study design), there were no clinically significant pharmacokinetic differences between subjects with moderate hepatic impairment and healthy subjects.

• PopPK analysis of Phase 2/3 trial data further indicates that the PK of raltegravir in Child Pugh B patients were not different from patients with normal hepatic function.

Labeling states: No dosage reduction for patients with moderate or mild hepatic impairment is recommended. The effect of severe hepatic impairment on the PK of the drug was not studied.

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022145s035,203045s012,205786s003lbl.pdf
To Summarize, Clinical Pharmacology Studies...

- Are conducted to gain a fundamental understanding of the pharmacokinetics (PK; exposure) and the pharmacodynamics (PD; biologic effect) of the drug.

- Provide useful information for the design of Phase 3 clinical trials (e.g., using dose-response and exposure-response analyses).

- Inform patient care
  - identification of appropriate dosing regimen(s) in relevant patient subpopulations
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