INTRODUCTION TO PHARMACOKINETICS (PK)

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Outline

• Definition & Relevance of Pharmacokinetics & Pharmacodynamics (PK/PD)

• Small v/s Large Molecules

• Fundamental Concepts of PK

• Q&A
What is Pharmacokinetics?

Pharmacokinetics (PK)
• What the body does to the drug

Absorption

Parent Drug
Metabolite
What is Pharmacokinetics?

Pharmacokinetics (PK)
• What the body does to the drug

Absorption
Distribution

Parent Drug
Metabolite
What is Pharmacokinetics?

Pharmacokinetics (PK)
• What the body does to the drug

ADME
PK Profiles Based on Route of Administration & Multiple Dosing

**AUC**: Area Under the Curve (measure of drug exposure)
What is Pharmacodynamics?

Pharmacodynamics (PD)
• What the drug does to the body

Transporter Occupancy of Duloxetine

[Graph showing SERT occupancy (%)]

JPET, April 2012, 341 (1) 137-145

Parent Drug
Active Metabolite
What is Pharmacodynamics?

Pharmacodynamics (PD)
• What the drug does to the body

Parent Drug
Active Metabolite

PD Effect of Proton Pump Inhibition

Rev Esp Enferm Dig. 2012 Jul;104(7):367-78

Transporter Occupancy of Duloxetine

JPET, April 2012, 341 (1) 137-145
What is Pharmacodynamics?

Pharmacodynamics (PD)
- What the drug does to the body

Parent Drug
- Active Metabolite

PD Effect of Proton Pump Inhibition

Transporter Occupancy of Duloxetine

PD Effect of Anti-Viral Drugs

Rev Esp Enferm Dig. 2012 Jul;104(7):367-78

JPET, April 2012, 341 (1) 137-145

http://annals.org/data/Journals/AIM/19857/6FF5.jpeg

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Fig. 1: Comparison of the intragastric pH profile of different PPIs. Mean 24-h intragastric pH with 4 PPIs versus baseline (49).
Has an Increased Understanding of PK/PD Helped?

### Attrition of drug candidates

- **n = 198**

- **39%** Pharmacokinetics
- **11%** Adverse effects in man
- **10%** Animal toxicity
- **5%** Commercial reasons
- **5%** Miscellaneous
- **5%** Lack of efficacy

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**Nature Reviews Drug Discovery** 2, 192-204 (March 2003)  
**Nature Reviews Drug Discovery** 14, 475-486 (2015)

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Better understanding of PK/PD principles seems to have shifted the drug attrition profile.
Why is PK/PD Important? A Recent Example

Selecting the right Drug and Dose in the right Population

Right Drug

Right Dose & Regimen

Right Population
Why is PK/PD Important? A Recent Example

Selecting the right Drug and Dose in the right Population

- Right Drug
- Right Dose & Regimen
- Right Population
Why is PK/PD Important? A Recent Example

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Recent Example from PD-1 Inhibitors in Oncology

PK → PD

Keytruda Approved for Any Solid Tumor With a Specific Genetic Marker

Keytruda (pembrolizumab) was granted an accelerated approval by the Food and Drug Administration (FDA) for the treatment of both adult and pediatric patients who have unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.

JASON M. BRODERICK @gastrooncology
PUBLISHED MAY 23, 2017

Journal for ImmunoTherapy of Cancer, 2017, 5:43
Small vs Large Molecule

Comparison of Molecular Mass of Small-Molecule (Chemical) Drugs Versus Large Biologics

- Enoxaparin 4500 (ave)
- G-CSF 18,800
- HGH 22,000
- EPO 30,400
- mAbs ~150,000

Ave=average; DA=Daltons; EPO=erythropoietin; G-CSF=granulocyte colony-stimulating factor; HGH=human growth hormone; mAbs=monoclonal antibodies.
### Small Molecule:
- Oral dosing route is generally preferred
- Half-life in body is typically in hours
- Additional PK considerations
  - Absorption characteristics from gut after oral dosing
  - First-pass metabolism (liver)
  - Potential for drug-drug interactions
  - Renal elimination
- No immunogenicity concerns
- Can access intra-cellular targets

### Large Molecule:
- IV/SC/IM dosing routes e.g. palivizumab (IM)
- Half-life in body is typically in days
- Additional PK considerations
  - Absorption characteristics from skin after SC dosing
  - No first-pass metabolism (liver)
  - Minimal potential for drug-drug interactions
  - Non-renal elimination mechanisms
- Immunogenicity concerns i.e. body can generate an immune response
- Primarily binds to extracellular targets
ADME - Absorption

Absorption is dependent on various physicochemical and physiological factors. The key parameters are
- Solubility in the GIT
- Permeability across the GI membrane

AAPS J. 2012 Jun; 14(2): 244–251
ADME - Absorption

Passive Diffusion v/s Active Transport

- Passive diffusion occurs based on a concentration gradient between intestinal lumen and portal vein concentrations.
- Active transport of drug molecules is mediated through transporter proteins with potential for capacity limitation (e.g. glucose & β-lactams).

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Extent of Absorption (Small Molecules Oral Dosing)

Extent of absorption i.e. Bioavailability ($F$)
- Fraction absorbed from lumen ($f_a$): Fraction of drug in the GI lumen that enters gut tissues
- Fraction absorbed from gut wall ($f_g$): Fraction of drug in gut wall that enters the portal vein i.e. fraction escaping gut metabolism
- Hepatic fraction absorbed ($f_h$): Fraction of drug in the portal vein that enters systemic circulation
- Hepatic Extraction Ratio ($ER$): Fraction of the drug that is extracted by the liver

$$F = f_a \cdot f_g \cdot f_h$$

$$f_h = (1 - ER)$$

F is relevant for SC or IM injections as well

_Nature Reviews Drug Discovery_ 2, 192-204 (March 2003)
Rate of Absorption (Small Molecules)

Rate of absorption i.e. how fast the drug enters systemic circulation

- Determines the time ($t_{\text{max}}$) to maximum concentration ($C_{\text{max}}$)
- For orally absorbed drugs, rate of absorption is generally described by a first-order rate constant, $k_a$. Units of $k_a$ is 1/time
- Inverse relationship of $k_a$ with $t_{\text{max}}$
Question 1

If the fraction of drug absorbed at each stage i.e. $f_a$, $f_g$, and $f_h$ is 50%, then what is the bioavailability ($F$)?

- A: 2500.0%
- B: 25.5%
- C: 12.5%

**HINT:**

\[ F = f_a \cdot f_g \cdot f_h \]
Question 1 Solution

If the fraction of drug absorbed at each stage i.e. $f_a$, $f_g$, and $f_h$ is 50%, then what is the bioavailability ($F$)?

• C: 12.5%

Explanation: $F = 0.5 \times 0.5 \times 0.5 = 0.125 \times 100 = 12.5\%$

• Drugs like vancomycin and gentamycin are polar with MWT $>400$ g/mole. These drugs have low $F$ due to low $f_a$
Volume of distribution ($V$) of a drug is an apparent volume that correlates amount and concentration of drug in the body.

\[
Concentration = \frac{Amount}{Volume}
\]

Typical physiological volumes include:

- Blood (4.5–5 L)
- Plasma (3 L)
- Blood cells (2 L)
- Intracellular water (27 L)
- Interstitial water (12 L)
- Extracellular water (15 L)

Source: Leon Shargel, Andrew B.C. Yu: Applied Biopharmaceutics & Pharmacokinetics, 7th Ed. www.accesspharmacy.com Copyright © McGraw-Hill Education. All rights reserved.
Why is “V” an Apparent Volume of Distribution?

Reported volumes greatly exceed physiological volumes.

Apparent “V” is determined by factors such as polarity, lipophilicity, and ionization state (pKa).

Volume of Distribution (V or V_d)

Volume of distribution is useful to calculate a loading dose

\[
\text{Concentration} = \frac{\text{Amount}}{\text{Volume}}
\]

\[C_{\text{time}=0} = \frac{\text{Dose}}{V}\]

I.V. Bolus
Volume of Distribution is Apparent

500 mg water 500 mL water

Conc_{\text{Water}} = 1 \text{ mg/mL};

Thus V = 500 mL

\[ \text{Volume} = \frac{\text{Amount}}{\text{Concentration}} \]
Volume of Distribution is Apparent

Concentration in Water:

- $\text{Concentration}_{\text{Water}} = 1 \text{ mg/mL}$;
- Thus $V = 500 \text{ mL}$

Concentration in Octanol:

- $\text{Concentration}_{\text{Water}} = 0.5 \text{ mg/mL}$;
- Thus $V = 1000 \text{ mL}$

$Volume = \frac{Amount}{Concentration}$
Volume of Distribution is Apparent

Partitioning contributes to an increase in apparent volume of distribution
- Lipophilic drugs that distribute extensively into tissues e.g. diazepam ($V = 168$ L)
- $V$ may approach physiological volumes e.g. monoclonal antibodies at high doses

$\text{Conc}_{\text{Water}} = 1 \text{ mg/mL}$;
Thus $V = 500 \text{ mL}$

$\text{Conc}_{\text{Water}} = 0.1 \text{ mg/mL}$;
Thus $V = 5000 \text{ mL}$

$\text{Gibaldi, M. 1984 "Biopharmaceutics and Clinical Pharmacokinetics", 3rd ed., Lea & Febiger, Chapter 12, page 214}$
PK Models – One or More Compartments

Poly-exponential PK indicates distribution phenomenon (non-specific or target-related)

A poly-exponential PK curve will require two or more compartments for adequate characterization of data
Question 2

Which drug has a larger volume of distribution?
Question 2: Solution

Which drug has a larger volume of distribution?
• Answer: Drug B

For any drug, a large apparent V is not necessarily a disadvantage. The absolute value of V is indicative of where the drug is distributed as well as physicochemical properties of the drug.
ADME – Metabolism & Elimination

• Hepatic & Gut Metabolism
  – CYP, UGT, etc… enzymes

• Renal Elimination

• Various terms referring to Elimination
  ➢ Clearance i.e. CL (Units: volume/time)
  ➢ For an organ, the maximal clearance is equal to blow flow to that organ
    ➢ Liver blood flow = 1.5 L/min
    ➢ Kidney blood flow = 1.2 L/min
    ➢ Glomerular Filtration Rate i.e. GFR = 0.1 L/min
  ➢ Elimination Rate Constant i.e. $k_{el}$ (Units: 1/time)
  ➢ Elimination half-life i.e. $t_{half}$ (Units: time)
Clearance (CL)

Drug CL is the volume that is cleared of a drug per unit of time.

- **t = 0**
- **e.g: t = 1 sec**
  - **CL = 3 drops/sec**
- **e.g: t = 1 sec**
  - **CL = 6 drops/sec**
Clearance at Steady-State (CL)

At steady-state, \( \text{Rate In} = \text{Rate Out} \)

For IV infusions, the dosing rate can be calculated using CL and required steady state concentration

\[
\text{Infusion}_\text{rate} = CL \cdot \text{Conc}_{ss}
\]
Total Clearance

Total CL is representative of the sum of all clearance mechanisms and organs

\[ \text{CL} = \text{CL}_{\text{gut}} + \text{CL}_{\text{liver}} + \text{CL}_{\text{kidney}} \]
Impact of Clearance on PK

$CL = \frac{Dose \cdot F}{AUC_{0-\inf}},$ where $F = 1$ for IV

CL is a determinant of drug exposure (AUC)
Metabolism

- Primarily impacts small molecules

- Four common type of reactions include:
  - Oxidation: Majorly mediated through cytochrome P450 (CYP) enzymes
  - Hydrolysis: Aspirin to salicylic acid and acetic acid
  - Reduction
  - Conjugation: Phase 2 reactions such as glucuronidation

- Metabolites are typically more polar and water soluble. Hence, lower reabsorption

- In some cases, metabolites may also be active
  - Prodrug: Codeine to morphine

- Characterizing metabolic profile of drugs is important to predict drug-drug interactions
Two drugs (A & B) are co-administered simultaneously. Drug A is known to **induce** the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

A. AUC of Drug B is lower  
B. AUC of both drugs A & B is lower  
C. No impact on AUC  
D. AUC of Drug B is higher
Question 3a: Solution

Two drugs (A & B) are co-administered simultaneously. Drug A is known to **induce** the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

A. AUC of Drug B is lower **(efficacy may be compromised)**
B. AUC of both drugs A & B is lower
C. No impact on AUC
D. AUC of Drug B is higher

Drug-drug interactions (DDI) are a major concern for drugs that are eliminated via the metabolic pathway. Enzyme induction may result in sub-therapeutic doses of drug.
Two drugs (A & B) are co-administered simultaneously. Drug A is known to inhibit the CYP3A4 enzyme. Drug B is primarily metabolized by CYP3A4 to an inactive metabolite. What is the impact on the PK (exposure) for both drugs compared to when these drugs are administered alone?

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A. AUC of Drug B is lower
B. AUC of both drugs A & B is lower
C. No impact on AUC
D. AUC of Drug B is higher (potential safety concern)

Drug-drug interactions (DDI) are a major concern for drugs that are eliminated via the metabolic pathway. This is especially true for drugs with a narrow therapeutic index.

An ideal drug candidate would have multiple elimination pathways, such that inhibiting any one pathway does not significantly impact exposures.
Assume same IV dose for drugs A & B

Q1: Which drug has higher CL?

1. A
2. B
3. A = B
Assume same IV dose for drugs A & B

Q1: Which drug has higher CL?

1. A
2. B
3. A = B

\[ CL = \frac{Dose \cdot F}{AUC_{0-\infty}}, \text{where } F = 1 \text{ for IV} \]
Assume same dose for drugs A & B
CL = 1.5 L/min

**Q2:** Which compound has greater tissue distribution?

1. A
2. B
Assume same dose for drugs A & B

CL = 1.5 L/min

**Q2**: Which compound has greater tissue distribution?

1. A
2. B
Assume same dose for drugs A & B

CL = 1.5 L/min

Q3: Is glomerular filtration the sole mechanism of elimination?

1. Yes
2. No

Hint: GFR is ~0.1 L/min
Assume same dose for drugs A & B

CL = 1.5 L/min

**Q3:** Is glomerular filtration the sole mechanism of elimination?

1. Yes
2. No

Hepatic metabolism could be a major and sole elimination pathway as well.
Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development
Examples Where Model-Based Analysis Has Helped Speed Up Drug Development

### Table III. Time savings of 2 to 18 months in phase II or III studies (6 out of 11 projects)

<table>
<thead>
<tr>
<th>Project</th>
<th>Method/gain</th>
<th>Time saving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immu #1</td>
<td>The relationships between pharmacokinetic and safety/efficacy were investigated in a phase I study conducted in patients. These results helped to skip phase II and were used to design the pivotal phase III study</td>
<td>12-18 months</td>
</tr>
<tr>
<td>ID #2</td>
<td>The selection of doses for a phase II study was based on a pathophysiological/pharmacokinetic-pharmacodynamic model. Without this model, another study (exploratory phase II) would have been necessary to ensure that the selected doses were well tolerated in this patient population</td>
<td>9-15 months</td>
</tr>
<tr>
<td>CVS #4</td>
<td>One higher dose concentration was added in the phase II study based on pharmacodynamic results in healthy volunteers. The results of the phase II study showed that, without this additional higher dose concentrations, the phase II study would have had to be repeated because of the inappropriate selection of doses</td>
<td>12 months</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th>MBDD approach adopted</th>
<th>Efficiencies gained over historical designs and analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>Omit phasella, model-based dose–response relationship, adaptive phase IIb design</td>
<td>2,750 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Hot flashes</td>
<td>Model-based dose–response relationship</td>
<td>1,000 Fewer patients</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>Prior data supplementation, model-based dose–response relationship, sequential design</td>
<td>760 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>Prior data supplementation, model-based dose–response relationship</td>
<td>120 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Gastroesophageal reflux</td>
<td>Model-based dose–response relationship</td>
<td>1,025 Fewer patients</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Model-based dose–response relationship</td>
<td>437 Fewer patients, increased probability of success</td>
</tr>
<tr>
<td>Global anxiety disorder</td>
<td>Omit phase IIb</td>
<td>260 Fewer patients, 1 year shorter study duration</td>
</tr>
<tr>
<td>Lower urinary tract symptoms</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Meta-analysis</td>
<td>Increased probability of success</td>
</tr>
</tbody>
</table>

MBDD, model-based drug development.

*This application is discussed further in the text as example 4, "Adaptive dose-finding phase II study designed using clinical trial simulations."

Clinical Pharmacology & Therapeutics
Volume 93, Issue 6, pages 502-514, 14 MAR 2013
PK Optimization in Drug Development

Optimization problem

- Poor systemic exposure
  - Distribution
    - Volume of distribution
    - Blood brain barrier
      - P-gp
      - MRP
      - OATP
      - OCTP
  - Transporters
    - Plasma protein binding
      - Cytochromes P-450
    - Which P-450?
    - Others
      - Which conjugate?
      - Glucuronide
      - Sulphate
      - Amino acids
    - 1A2, 2C9, 2C19, 2D6, 3A4
  - Regiospecificity
  - Lability
  - Affinity
- Clearance
  - Renal
  - Plasma
  - Hepatic
  - Metabolic
    - Biliary
    - pKa
    - Solubility
    - LogP/D
    - Membrane permeation
    - Paracellular
    - Transcellular
- First-pass clearance
- Absorption
  - Physicochemical properties
The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action. Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.
PK Analysis - NCA

Non-Compartmental Analysis
• Slope (k)
• Height ($C_{\text{max}}$)
• Area Under the Curve (AUC)

\[
CL = \frac{Dose \cdot F}{AUC_{0-\text{inf}}}, \text{where } F = 1 \text{ for IV}
\]

\[
F = \frac{AUC_{\text{po}}}{Dose_{\text{po}}} \cdot \frac{Dose_{\text{iv}}}{AUC_{\text{iv}}}
\]

\[
AUC_{0-\text{inf}} = AUC(0-t_n) + C(t_n)'/k
\]

\[
slope = -k \quad t_{1/2} = 0.693/k
\]

Ideally <25% extrapolated area

Elimination half-life
PK Analysis – Compartmental Evaluation

One compartment body model with first order absorption (e.g. Oral dose)

\[ C_p = \frac{Dose \cdot F \cdot k_a}{V \cdot (k_a - k_{el})} \left( e^{-k_{el} \cdot t} - e^{-k_a \cdot t} \right) \]

**Goal:** Estimate model parameters using non-linear regression
THANK YOU