Finding new drugs: A crap shoot

- **Discovery** (2–10 Years)
  - 20–80 Healthy Volunteers Used to Determine Safety and Dosage

- **Preclinical Testing**
  - Laboratory and Animal Testing

- **Phase I**
  - 100–300 Patient Volunteers Used to Look for Efficacy and Side Effects

- **Phase II**
  - 1,000–5,000 Patient Volunteers Used to Monitor Adverse Reactions to Long-Term Use

- **FDA Review Approval**

- **Additional Post-Marketing Testing**

- **Compound Success Rates by Stage**
  - 5,000–10,000 Screened
  - 250 Enter Preclinical Testing
  - 5 Enter Clinical Testing
  - 1 Approved by the FDA
Pharmacokinetic causes of drug failure

1. Poor bioavailability due to low aqueous solubility and/or high first pass metabolism

2. Inadequate duration of action due to high clearance and short half-life

3. Unanticipated drug interactions
   - Often revealed in Phase IIB and III
   - Results in variable PK properties
   - Undesirable effects on drug efficacy and safety
Clinical Drug Development

Reasons for attrition between 1990 and 2000

PK vs. PD

• Pharmacokinetics: the time course of a drug in humans
  – What the body does to the drug

• Pharmacodynamics: relationships between the dose or concentration of drug in the body and measured effects
  – What the drug does to the body
Why are pharmacokinetics important?

- Ultimate aim of drug therapy is to achieve efficacy without toxicity.
Absorption

• Movement of drug molecules across biological barriers from the site of administration to the blood stream

Route of administration

• Oral
• Parenteral: IV, SQ, IM
• Other: Inhalation, rectal, topical, transdermal

Bioavailability (F)

• The fraction of drug that reaches the systemic circulation
• Does not dictate rate of drug absorption
Absorption

First Pass Metabolism

• Blood supply of the upper GI tract passes through the liver before reaching the systemic circulation

• Drug may be metabolized by the gut wall and liver

\[
F = f_{\text{abs}} \cdot (1-f_g) \cdot (1-f_h)
\]
**pH and Drug Absorption**

- **For acidic drugs**
  - As the pH ↓, amount ionized drug ↓
  - Better absorbed at low pH
  - Most of drug in stomach is un-ionized, favoring absorption

- **For basic drugs**
  - As the pH ↓, amount ionized drug ↑
  - Better absorbed at higher pH
  - Most of the drug in the stomach is ionized

*Fig. 5-4. Diagram of gastrointestinal tract showing the variations in pH.*
Distribution

• Reversible transfer of drug from one location to another within the body

Blood flow through tissues
• Equilibration rapidly achieved with heart, lungs, kidneys and brain

Permeability of drug in the tissues
• Water soluble (blood and interstitial space) vs. fat soluble (fatty tissue)
• Drugs which pass the BBB into CNS are typically small and highly lipophilic
Protein Binding

- Drugs transported as free (unbound) drug and partly reversibly bound to blood components
- Only free drug is active
- 2 factors determine degree of protein binding
  1. Affinity of drug for plasma protein
     - Albumin-acidic
     - $\alpha_1$-acid glycoprotein-basic
  2. # of binding sites available
     - Drugs compete with other drugs, hormones or endogenous substances for sites
Volume that would be required in the body to contain the administered dose if that dose was evenly distributed at the concentration measured in plasma
Volume of Distribution

- **Low Vd (3-5L)** distribute in plasma
  - Drugs with very large MW or bound strongly to plasma proteins

- **Medium Vd (12-14)** distribute in extracellular space
  - Drugs with low MW but hydrophilic—can not cross lipid membranes to enter phase inside the cell

- **High Vd (>42L)** distribute in tissues
  - Low MW and hydrophobic
  - Drugs stored in fat may have Vd>TBF
Elimination

- The irreversible loss of drug from the site of measurement
- Metabolism: conversion of one chemical species to another
- Excretion: irreversible loss of chemically unchanged drug
Metabolism

• Enzymes involved in drug metabolism are present in many tissues
  – Can produce an active or inactive metabolite(s)
  – Overall goal to produce more polar compound

• Drug metabolism rates vary among patients
  – Genetic factors
  – Coexisting disorders (chronic liver disorders)
  – Drug interactions (especially those involving induction or inhibition of metabolism)
Phase I

• Involve formation of a new or modified functional group through oxidation, reduction, hydrolysis

• Most important enzyme system in this phase is Cytochrome P-450
  – Microsomal superfamily of isoenzymes that catalyze the oxidation of many drugs
  – Several families: 3A4, 2C9, 2C19, 1B6, etc.
  – Enzymes can be induced or inhibited by many drugs and substances
Cytochrome P450

- Most drugs metabolized by CYP450 3A4 isoenzymes (substrate)
- Some drugs induce (speed up) CYP450
  - ↓ in plasma concentration of other drugs which are substrates
- Some drugs inhibit (slow down) CYP450
  - ↑ in plasma concentration of other drugs which are substrates
Phase II Reactions

• Many Phase I metabolites are too lipophilic to be retained in the kidney tubules

• Conjugation reactions with an endogenous substrate or an amino acid results in more water soluble compounds
  – Glucuronic acid (glucuronidation)
  – Sulfuric acid (sulfation)
  – Acetic acid (acetylation)
Excretion

• Elimination of unchanged (not changed by the liver) or metabolite (changed by the liver) from the body

• Drugs may be eliminated kidneys, lungs, saliva, sweat, breast milk

• Enterohepatic Circulation
  – Drug excreted in the bile, stored in and released from the gallbladder, transit into the small intestine and then reabsorbed into the circulation
Renal Excretion

• Glomerular filtration
  – Small molecules/drugs filtered through the glomerulus
  – Drugs bound to plasma proteins are too large

• Tubular reabsorption
  – Lipid soluble drugs are reabsorbed from the lumen of the nephron back into the systemic circulation (ex: diuretics)

• Tubular secretion
  – Carrier-mediated active transport system that requires energy
  – Shows competition effects: probenecid (weak acid) competes for same system as penicillin thus ↓ rate of penicillin excretion

Excretion = Filtration – Reabsorption + Secretion
Renal Clearance

- Can be calculated to investigate the mechanism of drug excretion

<table>
<thead>
<tr>
<th>$CL_{\text{renal}}$</th>
<th>Clearance Mechanism</th>
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<tr>
<td>$\sim 120 \text{ ml/min}$</td>
<td>Filtration only</td>
</tr>
<tr>
<td>$&lt; 120 \text{ ml/min}$</td>
<td>Filtration and reabsorption</td>
</tr>
<tr>
<td>$&gt; 120 \text{ ml/min}$</td>
<td>Filtration and secretion</td>
</tr>
</tbody>
</table>
Clearance (CL)

- Measure of the ability of the body to eliminate drug
- Not an indicator of how much drug is removed but the volume of plasma cleared of drug in a given period of time
  - Expressed as a volume per unit time (mL/min or L/hr)

Half-life \( (t_{\frac{1}{2}}) \)

- Time for plasma drug concentration to be reduced by 50%
- 5 half-lives: after starting a drug dosing regimen before full effects will be seen (steady-state) and for a drug to be eliminated from the body
Total Clearance

- \( CL_{\text{total}} = CL_{\text{renal}} + CL_{\text{liver}} + CL_{\text{other}} \)
- Metabolic clearance \( (CL_{\text{liver}}) \) is dependent on drug metabolizing enzymes, while renal and biliary clearance are largely dependent on drug transporters
- Enzymes and transporters are subject to
  - Inhibition (most prevalent) or
  - Induction by other drugs
  - Genetic polymorphism (different subpopulations will be sensitive to DDI to different degrees)
Pre-Clinical and Clinical Studies

- Conduct SAD and MAD studies using an adequate dosing range
  - A minimum of 3 doses over a ≥ 10-fold range of doses
- Use an adequate sample size
- Collect samples over an appropriate time frame
- Examine concentration-response relationships instead of dosing until toxicity
How are the pharmacokinetics of a drug determined?
Sample Collection

- Invasive
  - Blood, plasma, serum
  - Spinal fluid, biopsy
  - Intensive vs. sparse sampling

- Noninvasive
  - Urine, feces, breath, saliva, breast milk, semen, vaginal secretions

- Most analytical methods designed for plasma analysis
Analytical Methods

High Performance Liquid Chromatography (HPLC)

Advantages
• Multiple analytes in one assay
• Works on polarity
• UPLC: better resolution and shorter run times

Disadvantages
• Background noise due to matrix
• Coelution difficult to detect
• Cannot determine the specific compound

Mass Spectrometry

Advantages
• Sensitive, Selective and Specific
• Ability to identify analytes
• Useful for small volumes

Disadvantages
• Very Expensive
• Difficult to run and maintain
Representative Pharmacokinetic Profile

- Peak Concentration ($C_{\text{max}}$)
- Absorption Phase
- Elimination Phase ($t_{1/2}$)
- Trough Concentration ($C_{\text{min}}$ at 24 hours)
- Area Under Curve ($AUC_{24}$)

Plasma Drug Conc (ng/mL) vs. Time Post Dose (h)
Assessment of Area-Under-the-Curve (AUC)

\[ AUC = \frac{(C_n + C_m) \times \Delta t_{(n,m)}}{2} \]

\[ AUC_1 = \frac{C_0 + C_1}{2} (t_1 - t_0) \]

\[ AUC_2 = \frac{C_1 + C_2}{2} (t_2 - t_1) \]

\[ AUC_3 = \frac{C_2 + C_3}{2} (t_3 - t_2) \]
Useful Equations

\[ CL = \frac{Dose}{AUC} \]

\[ k = \frac{\ln C_1 - \ln C_2}{t_2 - t_1} \]

\[ T_{1/2} = \frac{0.693}{K_e} \]

Relative \( F = \frac{F_A}{F_B} = \left( \frac{AUC_A}{AUC_B} \right) \times \left( \frac{Dose_B}{Dose_A} \right) \)

\[ AUC = \frac{(Cn + Cm) \times \Delta t_{n,m}}{2} \]

\[ Cp^0 = \frac{Dose}{V} \]

\[ t_{1/2} = \frac{0.693 \times Vd}{CL} \]

\[ AUC_{t_{last}} = \frac{Cp_{last}}{K_e} \]

\[ F = \left( \frac{AUC_{po}}{AUC_{iv}} \right) \times \left( \frac{Dose_{iv}}{Dose_{po}} \right) \]
Modeling Philosophies

- Describe data
- Quantify processes
- Explore mechanisms
- Make predictions

Can get AUC, CL, Vd, t1/2, etc. from NCA
- Can get these from modeling as well, and
  - assess covariate effects (age, weight, CL\textsubscript{cr}, etc.)
  - describe absorption characteristics
  - explore metabolite formation rate constants
  - simulate concentrations to predict effects
  - directly link PK model with response
One-Compartment Model

\[ R \quad \text{Vd} \quad \text{Ke} \]

Graph showing plasma drug concentration (ng/mL) over time post dose (h) from 0 to 24 hours. The concentration increases to a peak and then decreases. Below the graph, the text reads: "Before Administration" and "After Administration."
Two-Compartment Model

![Diagram of Two-Compartment Model]

- $R$
- $V_c$
- $K_{cp}$
- $V_p$
- $K_{pc}$
- $K_e$

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<th>Concentration - log</th>
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- Distribution Phase
- Elimination Phase
Dolutegravir Antiviral Activity

Mean Change from Baseline in HIV-1 RNA (log_{10} copies/mL)

**Dosing period** | **Follow-up period**
---|---

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Song I, et al. IAS 2009, Cape Town, poster #WEPEB250
Exposure-Response Relationship from Phase IIA

Song I, et al. IAS 2009, Cape Town, poster #WEPEB250
Relevance of Early-Phase PK/PD

• Understanding the pharmacokinetics and establishing pharmacodynamic relationships with these compounds is clinically vital to:
  – ensure proper dose selection during early phase development; go or no go decisions
  – evaluate the clinical significance of drug interactions
  – explore alternative dosing schedules
  – introduce new formulations with different pharmacokinetic characteristics
  – bring a drug into the pediatric population

![Graph showing the relationship between exposure and response](image)
• Understanding the basic principles of PK can assist in the drug discovery and development process

• Proper collection of PK data in animal studies can provide useful insight on ADME in humans

• Establishing concentration-response relationships is critical for proper dose selection
  – Animal models or humans
QUESTIONS?