Basic Concepts in Pharmacokinetics

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Objectives

1. Define pharmacokinetics
2. Describe absorption
3. Describe distribution
4. Describe elimination
Why do we study PK?

We administer drugs (dose) because we seek a certain effect (response), but a complex chain of events links the administered dose to the observed response.

Jusko, Ko, Ebling 1995
Drug concentration

PK is based on the analysis of drug concentrations.

After one or more doses (▲), the drug concentration in the desired matrix is measured (---).
The processes that characterize PK are summarized in the (L)ADME scheme.

1. Liberation
2. Absorption
3. Distribution
4. Metabolism
5. Excretion

Disposition

Elimination

Image from http://saladax.com
Absorption Distribution

Absorption

Dose of drug

Drug in blood

Drug at active site

Pharmacological effect

Distribution

Potential for a therapeutic effect

Elimination

Metabolism (M) + Excretion (E)

Need to maintain plasma concentration of a drug to achieve a therapeutic effect
Absorption

- Absorption - Passage of compound from the site of administration into the bloodstream (or lymph), usually across a membrane

- Systemic routes of drug administration:
  - **Intravascular** – placement of the drug directly into blood (intravenous (iv) or intra-arterial)
  - **Extravascular** – oral, sublingual, subcutaneous, intramuscular, rectal

- Most drugs administered extravascularly act systemically. In such cases, systemic absorption is a **prerequisite for efficacy**

- Local effect - systemic absorption is a safety issue.
Absorption after oral administration

Movement of unchanged drug from the site of administration to the site of measurement

Few potential sites of loss – contributes to decrease in systemic absorption
Bioavailability

- **Bioavailability (F)** refers to the extent of absorption of intact drug. Generally, refers to the fraction of an extravascularly administered dose that reaches the systemic circulation intact.

- BA studies provide useful information on the dosage/dosage regimen.

- BA studies provide information regarding the performance of a formulation.
Bioavailability

Relative F – comparison of F between formulations of a drug given by the same or different routes of administration

Absolute F is usually assessed with reference to an intravenous dose

Relative F

Absolute F

Figure 5
Bioequivalence (BE)

- **Bioequivalence**: Formulations containing the same dose of same chemical entity, generally in the same dosage form, intended to be interchangeable

- BE documentation may be useful to:
  - Link early and late phase clinical formulations
  - Compare clinical versus to-be-marketed formulation
  - Evaluate change of formulation (tablet vs. capsule)
  - Compare generic versus branded drug
Bioequivalence

A and B are the limits set (often ± 20%) around the reference product.

C-t profiles similar, NOT likely to cause clinically relevant differences in therapeutic and adverse effects!

Bioequivalent preparations generally considered to be therapeutically equivalent
Rate limiting steps for oral absorption

1. Disintegration time and dissolution rate
2. Movement through membranes
   a) perfusion or
   b) permeability limitations
3. Gastric emptying and intestinal transit
4. First-pass metabolism in the gut/liver

Can cause delay or loss of drug – alteration of drug concentration!
Absorption from solution: Movement through membrane

Absorption site

1. Transcellular
2. Paracellular
3. Efflux transporters

Blood and lymph
Absorption Distribution

Dose of drug

Drug in blood

Drug at active site

Pharmacological effect

Need to maintain plasma concentration of a drug to achieve a therapeutic effect

Distribution

Elimination

Metabolism (M) + Excretion (E)
Distribution

- Dose of drug administered
- ABSORPTION
- Drug concentration in systemic circulation
- DISTRIBUTION
- Drug in tissues of distribution
Distribution

- Volume of Distribution \( (V_d) \) = Apparent and hypothetical volume in which the drug is dispersed
- An equilibrium concept
- Relates measured plasma (or blood) drug concentration \( (C) \) to the amount of drug in the body \( (A) \)
- Important for drug dosage regimen to determine the loading dose

\[
V = \frac{A}{C}
\]
Distribution

- Value depends on reference fluid measured (plasma, blood, unbound drug)
- $C_b$, $C$ and $C_u$ can differ as a consequence of binding to cells and plasma proteins

However, at equilibrium:

$$A = V \cdot C = V_b \cdot C_b = V_u \cdot C_u$$

amount plasma blood plasma water
Relative size of various distribution volumes within a 70-kg individual

- Plasma: 4 liters.
- Interstitial volume: 10 liters.
- Intracellular volume: 28 liters
Distribution

- Vd: around 5 L.
- Very high molecular weight drugs, or drugs that bind to plasma proteins excessively
- Example: heparin 4L (3-5)
Distribution

Vd: between 4 and 14 L.

- Drugs that have a low molecular weight but are hydrophilic.

Example:
Atracuronium 11 L (8-15)
Distribution

- Diffusion to intracellular fluid. Vd equal to total body water.
  - Ethanol 38 L (34-41)
  - Alfentanil 56 L (35-77)

- Drug that binds strongly to tissues. Vd higher than total body water.
  - Fentanyl: 280 L
  - Propofol: 560 L
  - Digoxin: 385 L
### Volume of Distribution

<table>
<thead>
<tr>
<th>L/70kg</th>
<th>Drug</th>
<th>L/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>50,000</td>
<td>Quinacrine</td>
<td>500</td>
</tr>
<tr>
<td>10,000</td>
<td>Chloroquine</td>
<td>100</td>
</tr>
<tr>
<td>1000</td>
<td>Desmethylimipramine</td>
<td>10</td>
</tr>
<tr>
<td>100</td>
<td>Nortriptyline</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pethidine</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Propranolol</td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>Digitoxin</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Warfarin</td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>Tolbutamide</td>
<td></td>
</tr>
</tbody>
</table>

- Cautious interpretation of V that are in the range of physiological values:
- Drug can bind to plasma proteins, blood cells and tissue components.
Plasma Protein Binding

1. Generally reversible, very rapid

\[ D + P \rightleftharpoons DP \]

2. Extent of binding

\[ fu = \text{fraction of drug unbound in plasma (Cu/C)} \]
\[ 1 - fu = \text{fraction of drug bound} \]

3. fu varies widely among the drugs

_Total plasma concentration (C) usually measured rather than the more important unbound concentration (Cu)_
WHY IS UNBOUND CONCENTRATION IMPORTANT?

Assumption – only unbound drug diffuses into tissues, have pharmacological/toxicological effect and can be eliminated

Distribution

Plasma

$C_{\text{bound}}$

$Cu$

Tissue

$C_{\text{bound}T}$

$Cu_T$

Receptor

Elimination
\[ V = V_p + V_T \cdot \frac{fu}{fu_T} \]
Absorption

Dose of drug

Distribution

Drug in blood

Drug at active site

Pharmacological effect

Elimination

Metabolism (M) + Excretion (E)

Need to maintain plasma concentration of a drug to achieve a therapeutic effect
Elimination

Elimination = irreversible removal of the drug from the body

Metabolism
- liver and intestine as major sites
- main mechanism of drug elimination
- metabolites more polar than the parent drug and renally excreted

Excretion
- kidneys - renal
- liver – biliary excretion of drugs (hepatic)
- lungs - pulmonary (volatiles)
Concept of Clearance

PROPORTIONALITY CONSTANT

CLEARANCE is the parameter that relates rate of elimination to concentration:

\[
CL = \frac{\text{Rate of Elimination}}{C\text{ plasma}}
\]

Units of flow

\[
\frac{\text{mg/h}}{\text{mg/L}} = \text{L/h}
\]

If \( CL = 1\text{L/hr} \) and \( C = 0.5\text{ mg/L} \)  
Rate of elimination = 0.5 mg/hr - A steady-state concept
Concept of Clearance

CL is the apparent volume of plasma (or blood or plasma water) completely cleared of drug per unit of time.

Rate of elimination = CL · C = CL_b · C_b = CL_u · C_u

plasma       blood       plasma water

Value of clearance depends upon site of measurement
Dependence of elimination on both V and CL

- **Volume** of reservoir (V) = 1000 mL
- Dose = 10 mg
- Initial concentration = 10 mg/L
- Perfect filter (organ), removes all drug: Flow rate 100 mL/min
- **Clearance** (Volume of blood completely cleared of drug per unit of time = Flow Rate, Q = 100 ml/min)
- CL = 100 mL/min
- **Fractional rate of removal**, k = 100 mL/min/1000 mL = 0.1 or 10% /min
Dependence of elimination on both V and CL

Amount in body (A) \[ A = V \cdot C \]

Fractional elimination rate constant, \( k \), defined as:

\[ k = \frac{\text{Rate of elimination}}{\text{Amount}} = \frac{\text{CL} \cdot C}{V \cdot C} = \frac{\text{CL}}{V} \]

\[ \text{CL} = k \cdot V \]
Dependence of elimination on both distribution and CL

$$t_{1/2} = \frac{0.693}{CL}$$
The **elimination half-life** is defined as the time for the drug concentration to reach half of its value. Clinically interesting because intuitive, used to calculate when steady state is reached. It is a secondary parameter, which can be derived from CL and V.

Rate of elimination = CL*C

Remember that

\[ AUC = \int_{0}^{\infty} C(t)dt \]

Amount eliminated = \int_{0}^{\infty} CL.C(t)dt = CL \int_{0}^{\infty} C(t)dt = CL.AUC

Amount eliminated = Dose*F = CL*AUC

If CL is constant with time

\[ t_{1/2} = \frac{\ln(2) \cdot V}{CL} \]
1. Loss Across Organ of Elimination

Mass balance

Rate In: \( Q \cdot C_A \)

Rate Out: \( Q \cdot C_V \)

Rate of Elimination: \( Q \cdot C_A - Q \cdot C_V \)

Rate of Elimination = Rate In – Rate Out

Extraction ratio (E) = \( \frac{\text{Rate of Elim.}}{\text{Rate In}} = \frac{Q \cdot (C_A - C_V)}{Q \cdot C_A} = \frac{(C_A - C_V)}{C_A} \)
1. Loss Across Organ of Elimination

Rate In: $Q \cdot C_A$

Rate Out: $Q \cdot (1-E) \cdot C_A$

Rate of Elimination: $Q \cdot (E \cdot C_A)$

$$CL = \frac{\text{Rate of Elimination}}{\text{Entering concentration}} = \frac{Q \ (C_A - C_V)}{C_A} = Q \cdot E$$
Extraction ratio

\[ E = \frac{Q (C_A - C_V)}{C_A} \]

\[ E = 0 \rightarrow \text{No elimination} \]

\[ E = 1 \rightarrow \text{Complete elimination} \]

Typical blood flow values

Liver \hspace{1cm} 1300-1500 \text{ mL/min} \\
Kidney \hspace{1cm} 1100 \text{ mL/min} \\
Cardiac output \hspace{1cm} 6000 \text{ mL/min}
2. Additivity of Clearance

Liver and kidney are major organs of elimination

Rate of Elimination = Rate of Excretion + Rate of Hepatic Metabolism

\[ CL \cdot C = CL_R \cdot C + CL_H \cdot C \]

Dividing by C:

\[ CL = CL_R + CL_H \]
Hepatic Elimination

**MAJOR ROUTES:**
1. Metabolism
2. Biliary Excretion

Two blood supplies:

- Hepatic Portal Vein (1.1 L/min)
- Hepatic Artery (0.4 L/min)
- Hepatic vein (1.5 L/min)
Metabolism

- The drug is “changed” so it can be eliminated
- Generates more polar (water soluble), inactive metabolites
- Metabolites may still have potent biological activity (or may have toxic properties)
Metabolism

Metabolic enzymes and reactions

Phase 0
- Passive diffusion
- Carrier mediated uptake (OATP, OCT)

Phase I
- In most cases, generation or exposing of functional groups (e.g., -OH, -NH₂, -SH, -COOH)
- Reactions:
  - Oxidation
  - Reduction
  - Hydrolysis
  - Dealkylations
  - Deamination
- Enzymes:
  - Hydrolysis:
    - Esterase
    - Peptidase
    - Epoxide hydrolase
  - Reduction:
    - Azo and nitro reductase
    - Carbonyl reductase
    - Quinone reductase
  - Oxidation:
    - Cytochrome P450s (P450s or CYP)
    - Flavin-containing monoxygenases (FMO)
    - Monoamine oxidase (MAO)
    - Alcohol dehydrogenase
    - Aldehyde dehydrogenase and oxidase

Phase II
- Conjugation with endogenous substrates, large increase in drug polarity
- Reactions:
  - Glucuronide conjugation
  - Sulfate conjugation
  - Glutathione conjugation
  - Glutathione S-transferase (GST)
  - Amino acid conjugating enzymes
  - Methyl transferase
  - N-acetyltransferase
- Enzymes:
  - UDP-glucuronosyltransferases (UGT)
  - Sulphotransferase (ST)
  - Glutathione S-transferase (GST)

Phase III
- Sometimes referred to carrier mediated efflux/uptake (e.g., BCRP, MRP2, ABCB1,3, BSEP)
- Or additional conjugation

Non-polar → Polar
Metabolism

Phase I

- Converts the parent drug to a more polar metabolite by introducing or unmasking a functional group (-OH, -NH₂, -SH) – via oxidation, reduction, and hydrolysis

- Usually results in loss of pharmacological activity

- Sometimes may be equally or more active than parent

- Occurs primarily in the liver
Metabolism

Phase II (conjugation reactions)

- Subsequent reaction in which a covalent linkage is formed between the parent compound or Phase I metabolite and an endogenous substrate such as glucuronic acid, sulfate, acetate, or an amino acid.

- Highly polar – rapidly excreted in urine and feces.

- Usually inactive - notable exception is morphine 6-glucuronide.

- Usually occurs in liver and kidney (other organs sometimes involved).
Metabolism

Most oxidative metabolism occurs via CYP450 system
3. Hepatic extraction and clearance

- **Blood**: Unbound drug
  - a – binding to blood cells
  - b – binding to plasma proteins
  - c – transport into (and out of) hepatocytes
  - d – biliary excretion
  - e – metabolism

- **Hepatocyte**

- **Bile**

\[Q_{H,B}\]
Saturable kinetics can be approximated

• as 1st order for lower concentrations,
• and 0 order for higher concentrations, as the system saturates.

Described by the Michaelis-Menten equation:

\[
\frac{dC}{dt} = \frac{V_{\text{max}} \cdot C}{K_m + C}
\]

- Maximum rate
- Michaelis constant
- Concentration at which \(V_{\text{max}}/2\) is reached

*Image from http://en.wikipedia.com*
RENAL EXCRETION

Rate of excretion = $CL_R \cdot C$

RENNAL

$CL_R = \frac{\text{Rate of Urinary Excretion}}{C_{\text{plasma}}}$

$= \frac{V_{\text{urine}} \cdot C_{\text{urine}}}{C_{\text{midpoint}}}$

Units of flow = $L/h$
Renal Excretion

A net effect

1. Glomerular filtration
   GFR = 120 ml/min

2. Secretion – proximal tubule

3. Reabsorption – distal tubule

Urine 1-2 ml/min; pH = 5 – 7.8
Components of Renal Clearance

\[
\text{Rate of Excretion} = \left[ \text{Rate of Filtration} + \text{Rate of Secretion} \right] \times \left[ 1 - \text{Fraction reabsorbed} \right] / C_{\text{plasma}}
\]

\[
\text{CL}_R = (\text{CL}_{RF} + \text{CL}_{RS})(1 - F_R)
\]

- \(\text{CL}_{RF}\) – renal filtration clearance
- \(\text{CL}_{RS}\) – renal secretion clearance
- \(F_R\) - fraction of filtered and secreted drug reabsorbed
Glomerular Filtration

Passive process, only plasma water containing unbound drug (Cu) is filtered

GFR - Glomerular Filtration Rate
- usually constant and relatively independent of renal blood flow

\[
CL_{RF} = \frac{\text{Filtration Rate (Cu \cdot GFR)}}{\text{Plasma Concentration (C)}} = fu \cdot GFR
\]
GFR

- Determined using inulin or creatinine (fu=1 and not secreted or reabsorbed)
  
  Renal clearance, $\text{CL}_R = \text{fu} \cdot \text{GFR}$

- GFR depends on body size, gender and age

  Men (20 yr) – 120 ml/min per 1.73 m²

  Women (20 yr) – 110 ml/min per 1.73 m²

- GFR decreases by 1% per year after age 20
ACTIVE SECRETION

- Facilitates excretion
- Transporters exist for basic and acidic drugs

- Dissociation of plasma drug-protein complex as unbound drug is transported
- If no reabsorption occurs, all drug presented to the kidney may be excreted in the urine

\[ \text{CL}_{RS} \rightarrow Q_R \]

(1.1 L/min; e.g. PAH)
Excretion Rate

No reabsorption

Plasma Drug Conc.

Filtration

Secretion

Excretion

$T_M$
Lipophilicity and degree of ionization affect rate and extent of reabsorption. Equilibrium not always achieved, especially for polar strong acids and bases. Rate of reabsorption is important.
Urine pH varies: 4.5 – 7.6

Weak acids - $\text{CL}_R$ is pH-sensitive if:

\[ p\text{Ka} = 3 – 7.5 \quad \text{and} \quad \text{lipophilic in un-ionised form} \]

$p\text{Ka} < 3$ strong acids, mostly ionised - little reabsorbed

$p\text{Ka} > 7.5$ very weak acids, mostly un-ionised over urine pH range
Passive reabsorption – effect of pH

Urine pH varies: 4.5 – 7.6

**Weak bases** - $C_{LR}$ is pH-sensitive if:

\[ pKa = 6 \text{ – } 12 \]

\[ \text{and} \]

\[ \text{lipophilic in un-ionised form} \]

- $pKa < 6$ - mostly un-ionised over urine pH range
- $pKa > 12$ - mostly ionised; little reabsorbed
Effect of pH on urinary excretion

e.g. Amphetamine

<table>
<thead>
<tr>
<th>Urine pH</th>
<th>Urinary recovery unchanged 24h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (pH ≈ 6.3)</td>
<td>40%</td>
</tr>
<tr>
<td>Acidic (pH = 5.3)</td>
<td>70%</td>
</tr>
<tr>
<td>Alkaline (pH = 7.3)</td>
<td>3%</td>
</tr>
</tbody>
</table>
Passive reabsorption – effect of urine flow

- Flow-dependent CL$_R$ occurs when drug is reabsorbed.
- If equilibrium is achieved – a higher urine volume means a higher amount of drug in urine and higher CL$_R$

$$CL_R = \frac{\text{Rate of excretion}}{C_{\text{plasma}}}$$
$$= \frac{\text{Urine Flow} \times \text{Urine conc}}{C_{\text{plasma}}}$$

At equilibrium: $Cu = \text{Urine Conc}$

$$CL_R = fu \times \text{Urine Flow}$$
Drug overdose - forced diuresis and altered pH may be used to increase elimination of the drug.