An Introduction to Pharmacokinetics
OBJECTIVES

- Provide definitions
- Examine exponential processes and therapeutic windows
- Describe the absorption process and factors that affect it
- Examine factors affecting drug distribution
- Describe volume of distribution
- Examine routes of elimination
- Describe factors affecting renal and biliary elimination
- Describe some ‘minor’ routes of elimination
- Describe clearance and half-life
Mammillary Compartmental Models

1 - Compartment

Central 1

k

2 - Compartment

Central 1

Tissue 2

k_{2,1}

k_{1,2}

3 - Compartment

Deep Tissue 3

Centra 1

Tissue 2

k_{1,3}

k_{3,1}

k_{2,1}

k_{1,2}
Definitions

**Pharmacodynamics:**
- Study of the pharmacological response to a drug
- i.e. what the drug does to the body

**Pharmacokinetics:**
- Study of the movement of drugs within the body
  (Encompasses absorption, distribution & elimination)
- i.e. what the body does to the drug

Remember
For pharmacokinetic analysis the drug measurements need to be specific
Drug in

Gastrointestinal tract

Blood ↔ Tissues

Elimination

RMI Pharmacokinetics
Definitions

**Absorption:**
- Process by which a drug moves from the site of administration into the site of measurement

**Distribution:**
- Reversible transfer of a drug to and from the site of measurement
  - blood
  - plasma

**Elimination:**
- Irreversible transfer of a drug from the site of measurement
- Includes
  - Metabolic loss
  - Renal excretion
  - Biliary excretion (?) lungs
  - Sweat, milk, etc.
Toxic

C

Ineffective

Therapeutic

A

B

D

E

F

Plasma level

Time
Absorption

The process by which a drug moves from the site of administration to the site of measurement.
Some sites of Administration

Buccal cavity
Gastro-intestinal tract
Eyes
Skin
Nose
Lungs
Muscle
Rectum
Vagina

} Oral
In virtually all cases, a drug must be in aqueous solution before it can be absorbed.
Drug Transport

1) Passive Diffusion
2) Facilitative Diffusion
3) Active Transport

Passive Diffusion

- Moves from an area of high concentration to an area of low concentration
- Non-specific
- No competition
- No saturation
- No energy requirements
- Function also of surface area of absorption layer, diffusion coefficient ($\alpha \sqrt{\text{mol wt}}$) and partition coefficient (lipophilicity and thickness of membrane)
A diagram of a cell membrane

- Hydrophobic ends of lipid molecules
- Aqueous pores
- Protein
- Phospholipid
Drugs with ionisable groups can exist in ionised and unionised forms

For Acids: $[HA] + [H_2O] \rightleftharpoons [H_3O^+] + [A^-]$

For Bases: $[B] + [H_2O] \rightleftharpoons [OH^-] + [BH^+]$

PH – PARTITION HYPOThESIS
<table>
<thead>
<tr>
<th>Body Part</th>
<th>pH Range</th>
<th>Fluid Volume (litre/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouth</td>
<td>6.2 – 7.4</td>
<td>3 – 5</td>
</tr>
<tr>
<td>Stomach</td>
<td>1 – 3</td>
<td>6</td>
</tr>
<tr>
<td>Duodenum</td>
<td>5.5 – 7</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>6.5 – 7</td>
<td>10</td>
</tr>
<tr>
<td>Ileum</td>
<td>6 – 8</td>
<td></td>
</tr>
</tbody>
</table>
Is an acidic drug best absorbed from the stomach?
OPTIMIZATION OF SURFACE AREA IN THE SMALL INTESTINE
Effect of drugs which decrease or increase gastric emptying on the absorption of paracetamol
● **Bioavailability**
  - The rate and extent that intact drug (or active constituent if pro-drug) reaches the systemic circulation

● **Absolute Bioavailability**
  - When the total quantity of drug reaching the systemic circulation is measured—usually performed by reference to an intravenous dose when all the dose is administered into the systemic circulation

● **Relative Bioavailability**
  - When the bioavailability of the test formulation is compared to that of another formulation which is NOT administered directly into the systemic circulation
CALCULATION OF BIOAVAILABILITY FOR PLASMA

**Absolute Bioavailability (F) =**
\[
\frac{\text{AUC}_{\text{P.O.}} \times \text{DOSE}_{\text{I.V.}} \times 100\%}{\text{AUC}_{\text{I.V.}} \times \text{DOSE}_{\text{P.O.}}}
\]

**Relative Bioavailability =**
\[
\frac{\text{AUC}_{\text{P.O. (TEST)}} \times \text{DOSE}_{\text{P.O. (STAND)}} \times 100\%}{\text{AUC}_{\text{P.O. (STAND)}} \times \text{DOSE}_{\text{P.O. (TEST)}}}
\]
CALCULATION OF BIOAVAILABILITY FROM URINE

**Absolute Bioavailability** =
\[
\frac{U_{P.O.}}{U_{I.V.}} \times \frac{DOS{E}_{I.V.}}{DOS{E}_{P.O.}} \times 100\%
\]

**Relative Bioavailability** =
\[
\frac{U_{P.O.(TEST)}}{U_{P.O.(STAND)}} \times \frac{DOS{E}_{P.O.(STAND)}}{DOS{E}_{P.O.(TEST)}} \times 100\%
\]
Reasons for incomplete bioavailability:

1. Instability – Benzylpenicillin
2. Complexation – Tetracyclines and Ca^{++}
3. Gastrointestinal Transit – Insufficient time at absorptive surface
4. Microfloral metabolism
5. Gut wall metabolism
6. First pass hepatic metabolism
7. Biopharmaceutical factors

{First pass}
Rate limiting factors in drug absorption

DOSAGE FORM
Disintegration
GRANULES
Deaggregation
FINE PARTICLES

Dissolution
Dissolution
Dissolution

SOLUTION
GUT LUMEN

Transport
GUT WALL
Portal Blood Vessel
Areas of drug loss during absorption

- To Feces
- Metabolism
- Decomposition
- To Site of Measurement
- Liver
- Portal Vein
- Gut Wall
- Gut Lumen
- To Feces
- Metabolism

Fl, Fi, Fg
\[ F = F_{\text{INTESTINE}} \times F_{\text{GUT WALL}} \times F_{\text{LIVER}} \]
Elimination
Drug in
Gastrointestinal tract
Blood <-> Tissues
Elimination
A diagram of a cell membrane

- Phospholipid
- Hydrophobic ends of lipid molecules
- Aqueous pores
- Protein
DRUG PARTITION ACROSS A MEMBRANE CALCULATED FROM PH DIFFERENCES

For Acids
\[ R = \frac{\text{Conc on side 1}}{\text{Conc on side 2}} = \frac{1 + 10^{pH_1 - pK_a}}{1 + 10^{pH_2 - pK_a}} \]

For Bases
\[ R = \frac{\text{Conc on side 1}}{\text{Conc on side 2}} = \frac{1 + 10^{pK_a - pH_1}}{1 + 10^{pK_a - pH_2}} \]
Does physiological pH vary enough at different sites to influence drug distribution?
Perfusion rate limitation

Blood flow to different organs of man

Blood flow (ml min⁻¹)

- Brain
- Fat
- Heart
- Muscle
- Kidneys
- Liver
- Lungs
- Muscle
- Skin
Relative efflux of different drugs from cerebrospinal fluid

Diffusion rate limitation

Relative drug conc. (%) of initial level

Times (min)

Lipophilic

Hydrophilic

Antipyrine
Aminopyrine
Thiopental

5-Sulfosalicylic acid
Sulfaguanidine
Only unbound drug is available for distribution

Therefore

the ratio of binding to plasma and tissue protein is an important determinant in drug distribution
Types of protein to which compounds bind

<table>
<thead>
<tr>
<th>Protein</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Acidic</td>
</tr>
<tr>
<td>α1-acid glycoproteins</td>
<td>Basic</td>
</tr>
<tr>
<td>Globulins</td>
<td>Endogenous</td>
</tr>
</tbody>
</table>
Methods for the determination of plasma protein binding

<table>
<thead>
<tr>
<th>Method</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equilibrium dialysis</td>
<td>Generally good</td>
</tr>
<tr>
<td>Ultracentrifugation</td>
<td>Generally good</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Reasonable</td>
</tr>
<tr>
<td>Gel filtration</td>
<td>Poor</td>
</tr>
</tbody>
</table>
Determination of drug distribution:

- **Whole body autoradiography**
  1. Dose radioactive compound to animals
  2. Kill animal at required time after dosing
  3. Immediately freeze carcass in hexane/solid CO₂
  4. Cut thin sections of animal (e.g. with cryomicrotome)
  5. Expose sections to X-ray film

- **Quantitative tissue distribution studies**
  1. Dose radioactive compound animals
  2. Kill animals at required time after dosing
  3. Dissect out all tissues of interest
  4. Count radioactivity in each tissue by liquid scintillation counting
**Volume of distribution**

The term that relates the amount of drug within the body at any one time to its concentration (normally the concentration is measured)

<table>
<thead>
<tr>
<th>Type of volume term</th>
<th>Notation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial distribution volume</td>
<td>$V_i$</td>
<td>Measure of volume of the space that the drug equilibrates with instantaneously</td>
</tr>
<tr>
<td>Volume of distribution based on area</td>
<td>$V$</td>
<td>Volume of space that drug equilibrate with once distribution is complete</td>
</tr>
<tr>
<td>Steady-state vol. of distribution</td>
<td>$V_{ss}$</td>
<td>Volume of distribution at steady-state</td>
</tr>
</tbody>
</table>
**Vi (litre)** = \( \frac{\text{Dose (mg)}}{\text{Co (mg/litre)}} \) Initial distribution volume

\[ V = \frac{\text{Dose}}{\text{AUC} \cdot \lambda_Z} \]

Were \( \lambda_Z \) is the terminal exponential constant

**FOR BOLUS IV**

\[ V_{ss} = \text{Dose} \cdot \frac{(\text{AUMC})}{(\text{AUC})^2} \]

\[ = \text{Dose} \cdot \frac{\sum_{i=1}^{n} C_i}{\left(\frac{1}{\lambda_i}\right)^2} \]

\[ = \frac{\sum_{i=1}^{n} C_i}{\left(\sum_{i=1}^{n} \frac{C_i}{\lambda_i}\right)^2} \]
\[ V_D = V_P + V_T \quad \frac{f_u}{f_u T} \]

Where

- \( V_D \) = Volume of distribution
- \( V_P \) = Physical volume of plasma (3 litres for man)
- \( V_T \) = Physical volume of tissue
- \( f_u \) = Fraction of unbound drug in plasma
- \( f_u T \) = Fraction of unbound drug in tissue
The variation of volume of distribution, plotted on logarithmic scale, between different drugs in man.
Volume of body fluids in man

- Extracellular water
- Plasma
- Interstitial fluids
- Intracellular water
- Transcellular water
- Total body water

Volume (litre)
Elimination
The irreversible transfer of a drug from the site of measurement.

It includes:

- Metabolism
- Renal excretion
- Biliary excretion
- Lungs
- Sweat
- Milk
- etc.

Remember
For pharmacokinetic analysis the drug measurements need to be specific
Drug in

Gastrointestinal tract

Blood

Elimination

Tissues
Renal excretion
The effect of renal failure on the half-life of netilmicin in man
Stylized drawing of a kidney nephron

Bowman’s Capsule
(Glomerular filtration)

Proximal tubule
(Active secretion)

Distal tubule
(Passive absorption and excretion)

Collecting tubule
The effect of probenecid on the steady-state levels of cefotaxime and its metabolites
A diagram of a cell membrane

Phospholipid

Hydrophobic ends of lipid molecules

Aqueous pores

Protein
Drugs with ionisable groups can exist in ionised and unionised forms

For Acids $[HA] + [H_2O] \rightleftharpoons [H_3O^+] + [A^-]$

For Bases $[B] + [H_2O] \rightleftharpoons [OH^-] + [BH^+]$
Plasma levels of intravenous nicotine to subjects with alkaline or acid urine

![Graph showing plasma nicotine concentration over time for subjects with alkaline or acid urine. The graph indicates higher nicotine levels in alkaline urine compared to acid urine.]
Net rate of renal excretion = Rate of filtration + Rate of secretion - Rate of reabsorption
Biliary excretion

- Factors affecting biliary excretion of drugs
  - Polarity
  - Structural consideration
  - Molecular weight
Approximate molecular weight thresholds for biliary excretion

<table>
<thead>
<tr>
<th>Species</th>
<th>Molecular Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>325</td>
</tr>
<tr>
<td>Dog</td>
<td>325</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>400</td>
</tr>
<tr>
<td>Rabbit</td>
<td>475</td>
</tr>
<tr>
<td>Monkey</td>
<td>500</td>
</tr>
<tr>
<td>Man</td>
<td>500</td>
</tr>
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</table>
Enterohepatic circulation

Drug in

Gastrointestinal tract

Liver

Tissues

Elimination

Enterohepatic circulation
If biliary excretion occurs with subsequent enterohepatic circulation, has the drug been eliminated?
Elimination

The irreversible transfer of a drug from the site of measurement

Distribution

The reversible transfer of a drug to and from the site of measurement
Routes of elimination

- Metabolism
- Renal excretion
- Biliary excretion
- Lungs
- Sweat
- Mammary secretion (Milk)

Major

Minor
Plasma and milk profile of two analgesic drug dosed to a nursing mother

- Phenacetin in plasma
- Phenacetin in milk
- Acetaminophen in plasma
- Acetaminophen in milk

Time since drug administration (h):
- 2
- 4
- 6
- 8
- 10
- 12

Phenacetin or acetaminophen conc. (ng/ml):
- 1000
- 100
- 10

---

Plasma and milk profile of two analgesic drug dosed to a nursing mother

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Time since drug administration (h):
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- 10
- 12

Phenacetin or acetaminophen conc. (ng/ml):
- 1000
- 100
- 10
Pharmacokinetic parameters of elimination

- Clearance
- Renal Clearance
- Extraction Ratio
- Half-life
Clearance is the volume of blood, plasma or serum completely cleared of total or unbound drug per unit time.

Renal Clearance

Renal clearance is the volume of blood, plasma or serum completely cleared of total or unbound drug per unit time by kidneys.
Calculation of clearance

\[ \text{Cl} = \frac{F \cdot \text{Dose}}{\text{AUC}_{\infty}} \]

\[ \text{Cl}_R = \frac{U_{t_1-t_2}}{\text{AUC}_{t_1-t_2}} \]

Cl: Clearance
F: Bioavailability
AUC\(\infty\): Area under curve to infinite time
U: Amount excreted in urine
Bioavailability calculation based on clearance (Cl) concept

For a drug
\[ F_{iv} \times Cl = F_{po} \times Cl \]

but
\[ F_{iv} = 1 \]

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

Substituting
\[ \frac{Dose_{iv}}{AUC_{iv}} = \frac{F_{po} \times Dose_{po}}{AUC_{po}} \]

Rearrange
\[ F_{po} = \frac{AUC_{po}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{po}} \]
Determination of renal clearance by plotting excretion rate against Mid-point plasma level

![Graph showing the relationship between plasma drug concentration and excretion rate with the slope equal to ClR.](image)
Total Clearance = Metabolic Clearance + Biliary Clearance + Renal Clearance
If all of the radioactivity from a radiolabelled dose appears in urine can it be said the drug is renally cleared?

NO!
Extraction of drug by an eliminating organ

\[
\text{Extraction ratio (ER)} = \frac{C_{\text{IN}} - C_{\text{OUT}}}{C_{\text{IN}}} 
\]

\[
\text{Cl} = Q \cdot \text{ER} 
\]

\[
\text{CL}_B = Q \cdot \text{ER} 
\]

\[
\text{If } \text{ER} \geq 1 \quad \text{Then } \text{CL}_B = Q 
\]

- \(C_{\text{IN}}\) = Concentration of drug entering organ
- \(C_{\text{OUT}}\) = Concentration of drug leaving organ
- \(\text{Cl}\) = Clearance
- \(\text{ER}\) = Extraction Rate
- \(Q\) = Blood Flow
- \(\text{CL}_B\) = Blood Clearance

\(\text{Cl} = Q \cdot \text{ER}\)

\(\text{CL}_B = Q \cdot \text{ER}\)

\(\text{If } \text{ER} \geq 1 \quad \text{Then } \text{CL}_B = Q \cdot \text{ER}\)
A semilogarithmic plot of plasma levels of drug vs time showing determination of half-life.
A typical multiexponential drug-plasma curve
Calculation for the method of residuals

\[ F = A - W \]
\[ G = B - X \]
\[ H = C - Y \]
\[ I = D - Z \]
\[ t^{1/2} = \frac{0.693 \cdot V_D}{C_l} \]
Summary

- Pharmacokinetic terms defined
  - absorption / distribution / elimination
- The exponential process and therapeutic window described with emphasis on dosage regimen design
- Absorption described
- Factors affecting distribution described
  - pH / blood flow / polarity / binding to macromolecules
- Volume of distribution
  - Vi / V / Vss
- Routes of elimination including minor ones
- Factors affecting elimination
  - renal / biliary
- Parameters of elimination
  - clearance / half-life