Pharmacokinetics and Pharmacodynamics - the basics
Objectives

By the end of this session, you should be able to:

- Define pharmacodynamics and the four basic processes involved in pharmacokinetics

- Define parameters which can affect
  - Drug absorption
  - Drug distribution
  - Drug metabolism
  - Drug excretion

- Understand the concept of agonist and antagonist

- Define bioavailability, half life and therapeutic index and describe the relevance of these to drug action
What is Pharmacology?
Pharmacology is ............

The study of the properties of drugs and their interaction with living organisms, including viruses.
Pharmacokinetics v Pharmacodynamics

If Pharmacokinetics is what the body does to the drug then Pharmacodynamics is what the drug does to the body
Scientific Basis of Prescribing

Drug Therapy Decision

Drug designed into a dosage from that can be given to a patient

Drug gets into the body and reaches its site of action

Drug acts to produce its effect on the body

Drug leaves the body

Pharmacokinetics

Pharmacodynamics

Pharmacology

Is the effect on the body beneficial or harmful to the patient?

Therapeutics
Pharmacodynamics
Receptor Concept

• Tissues distinguish between chemical messengers (e.g. Hormones, neurotransmitters or drugs) via receptors

• Receptors are proteins on/in a cell wall

• Receptors bind with the chemical messenger

• Binding reaction transduces into a signal to the cell

• Cell then responds accordingly
Receptor Concept

Drug molecule 'locking' onto a receptor site to form a drug–receptor complex.

receptor site

Cell membrane
Agonist

A chemical that binds to a receptor and elicits an appropriate response.

Antagonist

A chemical that binds to a receptor but elicits no response and blocks access to the receptor by an agonist.
Take a look at a YouTube clip explaining the theory of agonists and antagonists..........

PS This is a Canadian clip and so Epinephrine is what we know as Adrenaline!

Receptor Concept
Specificity

‘Ability of a drug to combine with a particular type of receptor’.

Ideally a drug would only bind to the receptor(s) that cause(s) the desired effect.
E.g. drug for pain would only bind to ‘pain’ receptors.

Unfortunately there are virtually no drugs that are totally specific for just one type of receptor. Hence, unwanted effects and side-effects.
Example

- Beta ($\beta$) receptors – $B_1$, $B_2$ and $B_3$
  - $B_1$ receptors_ heart, kidney, stomach
  - $B_2$ receptors_ smooth muscle, fat cells, uterus, bladder, gastro-intestinal tract, salivary glands, kidneys, lungs and brain
  - $B_3$ receptors_ fat cells

‘Beta-blockers’ – block beta receptors.
e.g. Atenolol = heart AND lungs.
Celiprolol = more ‘cardioselective’
Affinity

‘The strength of the interaction between a drug and the binding site of the receptor’.

Closer the fit between the 2 molecules the higher number of bonds formed, the greater the attraction and the greater the affinity.
Pharmacokinetics

.......what the body does to the drug
Why is the study of pharmacokinetics important?

If a drug is going to have an effect in the body it needs to be present:

• In the right place
• At the right concentration
• For the right amount of time
Knowledge of pharmacokinetic data about a drug tells us:

• What dose to give
• How often to give it
• How to change the dose/route in certain medical conditions
• How some drug interactions occur
The licensed particulars for a drug can be found within the Summary of Product characteristics on the following website:

www.medicines.org.uk/emc
Pharmacokinetic Processes

Extravascular Administration

Gut Wall

Blood

DISTRIBUTION

Body Tissues

METABOLISM

Liver

EXCRETION

Kidney

Intravascular Administration

ABSORPTION
List as many different routes of drug administration that you can think of....
## Routes of Administration (1)

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Mouth, GI tract</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Under tongue</td>
</tr>
<tr>
<td>Buccal</td>
<td>Oral mucosa</td>
</tr>
<tr>
<td>Intra-ocular</td>
<td>Eyes</td>
</tr>
<tr>
<td>Topical</td>
<td>Skin</td>
</tr>
<tr>
<td>Rectal</td>
<td>Rectum</td>
</tr>
<tr>
<td>Vaginal</td>
<td>Vagina</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>Nasal passages or lungs</td>
</tr>
</tbody>
</table>
## Routes of Administration (2)

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intradermal</td>
<td>Into skin layers</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Directly into venous blood</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>Muscles</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Into blood from skin layers</td>
</tr>
<tr>
<td>Epidural</td>
<td>Epidural space</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Directly into cerebro-spinal fluid</td>
</tr>
<tr>
<td>Intraoseos</td>
<td>Into the bone</td>
</tr>
<tr>
<td>Intra-uterine</td>
<td>Into the uterus</td>
</tr>
</tbody>
</table>
# Routes of Administration (3)

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-conjunctival</td>
<td>Conjunctiva of eye</td>
</tr>
<tr>
<td>Intraspinal</td>
<td>Spine</td>
</tr>
<tr>
<td>Intraarticular</td>
<td>Joints</td>
</tr>
<tr>
<td>Intraarterial</td>
<td>Arteries</td>
</tr>
<tr>
<td>Intracardiac</td>
<td>Heart</td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Peritoneal cavity</td>
</tr>
<tr>
<td>Intrapleural</td>
<td>Lungs</td>
</tr>
<tr>
<td>Sublabial</td>
<td>Labia</td>
</tr>
<tr>
<td>Perispinal</td>
<td>Spine</td>
</tr>
</tbody>
</table>
## Routes of Administration (4)

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Site of absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravesical</td>
<td>Into the bladder</td>
</tr>
<tr>
<td>Intracavernosal</td>
<td>Into Corpus Cavernosum</td>
</tr>
<tr>
<td>Intraurethral</td>
<td>Into urethra</td>
</tr>
<tr>
<td>Intrapleural</td>
<td>In the pleural cavity</td>
</tr>
<tr>
<td>Transscleral</td>
<td>Through the sclera to the retina</td>
</tr>
<tr>
<td>Transmucosal</td>
<td>Across mucosa</td>
</tr>
<tr>
<td>Endotracheal</td>
<td>Within/through the trachea</td>
</tr>
<tr>
<td>Intracerebroventricular</td>
<td>Ventricular system of the brain</td>
</tr>
<tr>
<td>Intrabursal</td>
<td>Bursae</td>
</tr>
</tbody>
</table>
Pharmacokinetic processes

- **A** bsorption
- **D** istribution
- **M** etabolism
- **E** limination

“The journey of medication through the body”

Click on here to watch a YouTube clip on the basic concepts of ADME.
Oral route:
What would the graph of blood level against time look like?
What is happening in these two time frames?
IV route:
What would the graph of blood level against time look like?
Cell Membrane

Click here to watch a Youtube clip on Cell Membranes

+ve charged Hydrophlic heads
Mechanisms of absorption of drugs from

• Diffusion
  • Passive
  • Facilitated

• Active Transport

• Endocytosis and exocytosis
Diffusion

• Passive Diffusion

• Facilitated Diffusion

Click here to watch a YouTube clip on Diffusion
Passive Diffusion

• Concentration gradient across a membrane
  • Drug moves from region of high concentration to lower concentration
  • There is NO carrier
• Majority of drugs enter the body via this mechanism
• Water soluble drugs cross the membrane via aqueous channels or pores
• Lipid soluble drugs move across by dissolving into the membrane’s lipid layers
Click here to watch a YouTube clip on Passive versus Active Transport
Facilitated Diffusion

- Other agents can cross a membrane via transport proteins that facilitate the passage of larger molecules.
- Concentration gradient across a membrane:
  - Drug moves from region of high concentration to lower concentration.
  - There is NO carrier.
- Transport Proteins undergo conformational changes.
- Does not require energy.
- E.g. Glucose moving from blood into cells after a meal.
Click here to watch a YouTube clip on Facilitated Diffusion
Active Transport

- Involves specific **Carrier Proteins** that span the membrane
- A few drugs that resemble naturally occurring metabolites are transported via this mechanism
- Energy-dependent (ATP -> ADP)
- Can move drugs from Low to High concentration
- Competitive and can be saturated
• Click here to watch a YouTube clip on the Transport Pump:

• Click here to watch a YouTube clip on ATP:
Endocytosis & Exocytosis

• Transport drugs of exceptionally large size across the cell membrane

• **Endocytosis** – cell membrane engulfs the drug molecule and transports into the cell by “pinching” off the drug filled vesicle. E.g. Vitamin B12 going into cells.

• **Exocytosis** – is the reverse of endocytosis and is used to by cells to secrete many substances by a similar vesicle process.
  • E.g. Noradrenaline being released from cells.
Click here to watch a YouTube clip on :-

Endocytosis
Click here to watch a YouTube clip on:-

Exocytosis
What factors affect drug absorption?
Factors affecting drug absorption

- **Food/Acidity**
  - Enhance e.g. ketoconazole
  - Impair e.g. tetracyclines, penicillin V

- **Formulation**
  - Enteric coated / Slow release

- **Route of administration**
  - IV = complete absorption
  - Oral = partial absorption

- **Lack of specific receptor needed for absorption**
  - e.g. Vitamin B12 absorption

- **PH of blood**
  - Acidosis / Alkalosis
• **Site of drug absorption**
  - If drug is absorbed from stomach, could Bypass absorption site e.g. E/C preparations, PEJ tubes

• **Malabsorption syndromes**
  - e.g. cystic fibrosis

• **GI motility**
  - e.g. rapid GI transit – Crohn’s disease, pro-kinetic drugs

• **Inactivation of drug in gut or liver**
  - e.g.-Insulin destroyed by proteolytic enzymes

• **Increased blood flow:**
  - Deltoid>gluteal

• **Drug interactions:**
  - e.g. Ciprofloxacin + calcium or iron

• **Pre-existing medical conditions**
  - e.g. heart failure
Bioavailability

• The fraction of the administered dose of the unchanged drug that reaches the systemic circulation available to have an effect

• Affected by:
  • Dosage form
  • Dissolution and absorption of drug
  • Route of administration
  • Stability of the drug in the GI tract (if oral route)
  • Extent of drug metabolism before reaching systemic circulation e.g. First Pass metabolism
  • Presence of food/drugs in GI tract
What factors affect drug distribution?
Factors affecting drug distribution

A) Blood flow
   - Reduced blood flow e.g. diabetics
   - Which organ?

B) Capillary permeability
   - Capillary structure
   - Chemical nature of drug +ve/-ve?

C) Binding of drugs to plasma tissues & proteins

D) Volume of Distribution
Order of blood perfusion?

- Heart
- Skeletal muscle
- Lungs
- Kidneys
- Brain
- Liver
- Adipose tissue
- Skin & viscera
Brain > Lungs > Liver > Heart > Kidneys > Skeletal Muscle > Adipose Tissue, Skin and Viscera
Volume of Distribution

- Drugs are distributed unevenly between various body fluids and tissues according to their physical and chemical properties.

- For example, gentamicin:
  - Very good water solubility
  - Very poor lipid solubility

Gentamicin stays mainly in plasma and body water.
Once a drug enters the body (any route), distributes to :-

- **Plasma Compartment**
  - Very large molecular weight
  - Protein bound
  - 6% of body weight *(4L)*

- **Extracellular Fluid (14L)**
  - Low molecular weight
  - Hydrophilic (Lipophobic)

- **Total Body Water (42L)**
  - Low molecular weight
  - Hydrophobic (Lipophilic)
Volume of distribution (Vd)

‘Measurement of the extent to which a drug is dissolved throughout the body’s compartments.’

We have to estimate because we can only measure the drug concentration in the blood stream
Imagine the body was a bucket:

- **Dose In**
- **Overflow into tissues**
- **Blood stream**
- **Tissues**

**Excretion**
A low volume of distribution tells us that the drug is mainly confined to blood and body water.

Very little has ‘overflowed’ into the tissues.
A high volume of distribution tells us that the drug is widely distributed to the tissues.

A lot has ‘overflowed’ into the tissues.
Volume of Distribution

• Vd will vary between different drugs according to:
  • Lipid and water solubility
    • High lipid solubility lets the drug cross membranes
  • Plasma or tissue protein binding properties
    • High protein binding leaves less drug circulating in the plasma
Uses of volume of distribution

- If a drug is highly distributed to the tissues the first few doses disappear immediately from the blood stream
- Loading doses are required to fill up the tissues and the plasma
- Important if the site of drug action is in the tissues

Examples:
- Amiodarone
- Digoxin
Imagine a bucket with a leak

You give a loading dose to fill up the bucket in the first place

After that you only need to give enough to replace the amount leaking out. This is the maintenance dose.
Knowing the Volume of Distribution can help you calculate the dose needed to achieve a critical plasma concentration.
Plasma Protein Binding

- Many drugs bound to circulating plasma proteins such as albumin
- Only free drug can act at receptor site
Highly Protein Bound Drugs

- > 95% bound
  - Thyroxine
  - Warfarin
  - Diazepam
  - Frusemide
  - Heparin
  - Imipramine
  - Amitriptyline

- > 90% but < 95% bound
  - Glibenclamide
  - Phenytoin
  - Propranolol
  - Sodium Valproate

Changes in plasma protein binding are significant for drugs which are greater than 90% bound to plasma proteins
Factors which can INCREASE the fraction of unbound (free) drug:

• Renal impairment => leaking albumin
• Low plasma albumin levels (<20-25g/L)
  • E.g. chronic liver disease, malnutrition
• Late pregnancy
  • Increased albumin production, but diluted by increased blood volume
• Displacement from binding site by other drugs
  • e.g aspirin, sodium valproate, sulphonamides,
• Saturability of plasma protein binding within therapeutic range
  • e.g. phenytoin
What factors affect drug metabolism?
Factors affecting drug metabolism

Main site of drug metabolism = LIVER

- Drug metabolism can be affected by:
  - “First Pass” effect
  - Hepatic blood flow
  - Liver disease
“First Pass” Metabolism

- Drugs absorbed from GI tract pass into the blood stream
- Blood travels IMMEDIATELY to the liver
- Some drugs are inactivated the first time they pass through the liver
- Affects drug dose given by different routes:
  - Example: Propranolol
    - If given IV, the dose is 1mg
    - If given PO, the dose is 40mg
- Affects possible routes of administration
  - Example: GTN cannot be given orally except by by-passing the liver (S/L or buccal tablets)
The hepatic portal system

Arterial system to all of body → Heart → Liver

Hepatic portal vein

Water

Mouth → esophagus → Stomach → Small intestine → Large intestine → Rectum → anus →

Gastric glands

Secretions of pancreas and liver

digested food

pH < 1

pH 8

http://www.ultranet.com/~jkimball/BiologyPages/G/GITract.html
Hepatic Extraction Ratio:

Measure of the extent to which a drug is removed by the liver from incoming blood
If a drug has a high hepatic extraction ratio, drug clearance is highly affected by hepatic blood flow

- Morphine
- GTN
- Propranolol
- Pethidine
- Lignocaine

Types of patient affected: Alcoholic liver disease, Cirrhosis
If a drug has a low hepatic extraction ratio, drug clearance is independent of hepatic blood flow, but depends on the metabolic capacity of the liver.

- Diazepam
- Phenobarbitone
- Phenytoin
- Theophylline
- Warfarin

Types of patient affected: Paracetamol overdose, Hepatitis.
Factors affecting drug metabolism

- Genetic factors (Pharmacogenetics)
- Other drugs
  - hepatic enzyme inducers
  - hepatic enzyme inhibitors
- Age
  - Impaired hepatic enzyme activity
    - Elderly
    - Children < 6 months (especially premature babies)
Enzyme Inducing Drugs

• Enhance the (production of) liver enzymes which break down drugs

• Faster rate of drug breakdown

• Larger dose of affected drug needed to get the same clinical effect
Enzyme Inducing Drugs

- Phenytoin
- Phenobarbitone
- Carbamazepine
- Rifampicin
- Griseofulvin
- Chronic alcohol intake
- Smoking
Enzyme Inhibiting Drugs

• Inhibit the enzymes which break down drugs

• Decreased rate of drug breakdown

• Smaller dose of affected drug needed to produce the same clinical effect
Enzyme Inhibitors

- Erythromycin
- Ciprofloxacin
- Metronidazole
- Chloramphenicol
- Sulphonamides
- Acute alcohol
- Allopurinol
- Phenylbutazone
- Isoniazid

- Sodium valproate
- Oral contraceptives
- Cimetidine
- Omeprazole
- Calcium channel blockers
- Amiodarone
- Dextropropoxyphene
- Fluconazole
What factors affect drug excretion?
Factors affecting drug excretion

Main site of drug excretion: KIDNEYS

Impaired renal function = impaired drug excretion if drug is mainly renally excreted

- Drugs also excreted in bile, sweat, lungs, breast milk, tears, genital secretions, saliva
Factors affecting drug excretion

- Renal drug elimination depends on:
  - Blood flow to kidney (normal 1500ml/min)
  - Glomerular filtration rate (normal 120mls/min)
  - Urine flow rate and pH which indirectly alter
    - Passive reabsorption
    - Active tubular secretion

Patients with poor renal function will not eliminate renally excreted drugs very well
Which patients will have altered renal function?

- Elderly
- Neonates
- Patients with renal impairment
  - Acute
  - Chronic
Significance

- Care with renally excreted drugs
- Care with drugs with a narrow therapeutic index
  - Example: digoxin
- Care with drugs which produce active metabolites
  - Benzodiazepines (diazepam + chlordiazepoxide)
  - Antipsychotics (risperidone, thioridazine)
  - Opioids (morphine, pethidine, dextropropoxyphene)
- Care with drugs that may further reduce renal function
  - NSAIDs
Half Life

Half life is the time required to reduce the plasma concentration of a drug to half of its original value and is usually measured in hours.
Half-life is the time taken for the concentration of drug in blood to fall by a half.
Significance

• Say a patient is taking a drug and has a toxic blood level of 16mg/L

• If......
  • The blood level you want is 2mg/L
  • Half life is 8 hours

How long will it take for the blood level to fall back to the level you want?
Answer...

Half life = time taken for blood level to reduce by 50%

Therefore:
16mg to 8mg = 8 hours

8mg to 4 mg = 8 hours

4mg to 2mg = 8 hours

Total: 24 hours
Time to Steady State

- Time to steady state (Tss) depends on half life

\[ Tss = 4 - 5 \times t^{1/2} \]

- Half life DOES NOT depend on:
  - Dose
  - Dosage Interval
Effect of half life on plasma concentration at the beginning of dosing
Effect of half life on plasma concentration at the end of dosing
Therapeutic index

- Therapeutic index is the difference between
  - plasma concentration that produces desired effect
  - plasma concentration that causes adverse effects

- Drugs with a narrow therapeutic index
  - digoxin, gentamicin, carbamazepine, phenytoin, lithium and theophylline

- Plasma concentration measurement
  - to ensure suppression of seizures by phenytoin
  - to prevent toxicity with gentamicin
Objectives:

So, can you:

• Define pharmacodynamics and the four basic processes involved in pharmacokinetics

• Define parameters which can affect
  • Drug absorption
  • Drug distribution
  • Drug metabolism
  • Drug excretion

• Understand the concept of agonist and antagonist

• Define bioavailability, half life and therapeutic index and describe the relevance of these to drug action?