INTRODUCTION TO PHARMACOLOGY

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Pharmacology
Pharmacokinetics
Time course of drug concentration in the body. The processes that determine time course are:
A - Absorption
D - Distribution
M - Metabolism
E - Excretion

Pharmacodynamics
Concentration / effect relationship
Drugs and Drug Targets

• A **drug** is a chemical that alters the function of a physiological system in a specific way.

• Molecules or structures that drugs interact with are **drug targets**.

• **Receptors** are an important subtype of drug target.
  – Proteins that recognise and respond to chemical signals.
Molecular Drug Targets

**PHYSIOLOGICAL EFFECTS**

**MOLECULAR TARGETS**

**ENZYMES**
- eg. COX 1 and 2 (aspirin)

**MEMBRANE RECEPTORS**
- eg. GABA<sub>A</sub> receptor (diazepam)

**INTRACELLULAR RECEPTORS**
- eg. Oestrogen receptor (oestrogen)

**ION CHANNELS**
- eg. Calcium channels (verapamil)

**NUCLEIC ACIDS**
- eg. DNA (cyclophosphamide)

**STRUCTURAL PROTEINS**
- eg. Tubulin (colchicine)

**TRANSPORT PROTEINS**
- eg. Noradrenaline uptake (cocaine)
Drug – Target Interaction

• The interaction of a drug with its target will either make something happen ‘switch on’ or stop something from happening ‘switch off’.

  – Examples of drugs that ‘switch on’ processes:
    • Morphine – opioid receptor agonist
    • Adrenaline – adrenoceptor agonist

  – Examples of drugs that ‘switch off’ processes:
    • Verapamil – calcium channels blocker
    • Omeprazole – proton pump inhibitor
Desirable Drug Properties

**Effective**
- High quality evidence

**Safe**
- High therapeutic index
- Selectivity
- Predictability (low intra- and inter-individual variability)
- Freedom from drug interactions
- Reversible action

**Other**
- Easily administered
- Low cost
- Chemically stable
- Simple generic name
Drug Discovery and Development

Drug Discovery

Drug Development

Lead Compounds

NME Marketed
Drugs Discovery: Serendipity

“Chance favors the prepared mind” - Pasteur
Serendipity: Penicillin

• Penicillin mould inhibits growth of staphylococci (Flemming, 1928)

• Florey isolates semi-pure antibiotic in 1940
Natural Products: Opioids

- **Opium Poppy**
  - Morphine
  - Codeine
  - Heroin
Rational Drug Discovery

1. Identify molecular target of value
2. Develop high-throughput assay and screen a large number of chemicals
Rational Drug Discovery: Identify molecular target of value

Pathways of Parkinson’s Disease

New Technologies

Druggable
Rational Drug Discovery

- Modify an endogenous agonist

Histamine ➔ Cimetidine
Rational Drug Discovery

• Structure-based discovery

http://pubs.acs.org/cen/coverstory/7923/7923drugdesign.html
Rational Drug Discovery: High-throughput Screening


Miniaturization: http://www.tdi.ox.ac.uk/high-throughput-screening-2
Discovery & Development Stages

1. Target Identification
2. Screening
3. Lead Optimization
4. Preclinical development
5. Clinical development Phase 1-3
Lead Optimization

• Synthesis of analogues
  – small variations to lead compound

• Aim to improve
  – Interaction with the target
  – PK / toxicity / physicochemical

• Understand structure-activity relationships
  – 3D structure of target helpful
Pre-clinical Testing

• Extensive testing of a small number of optimized lead compounds
• Animal models
  – Rats mainly but others as well (e.g. dog)
• Extensive safety testing:
  – Acute, sub-acute, chronic toxicology
  – Reproductive toxicology
  – Hepatotoxicity
  – Genetic toxicology
  – Carcinogenicity
• Manufacture in preparation for clinical trials
Clinical Testing

- Investigational New Drug application to FDA
- Phase 1 (Is it safe? What is the best dose?)
  - Small group of health volunteers
- Phase 2 (Does it work?)
  - Relatively small group of patients
- Phase 3 (How well does it work?)
  - Large group of patients
  - Randomized controlled trial
Drug Development Timeline

PRE-DISCOVERY: BASIC RESEARCH AND SCREENING

5,000 - 10,000 COMPOUNDS

250

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drug Discovery

Preclinical

Clinical Trials

Drugs discovered in preclinical trials are tested on 5 volunteers.

Phase 1 Clinical Trials:

20 - 100 volunteers

Phase 2 Clinical Trials:

100 - 500 volunteers

Phase 3 Clinical Trials:

1,000 - 5,000 volunteers

FDA Review

Scale-Up to Manufacturing

Ongoing Research and Monitoring

Cost $1.2 billion US

PhRMA Profile 2013
Drug Scheduling

**Benefit of easier access**

- Comparative efficacy

**Potential harms of easier access**

- Frequency / severity of adverse effects
- Potential for abuse
- Potential for masking undiagnosed condition
- Importance of professional interaction

http://www.australianprescriber.com/magazine/20/1/12/3
Examples of Scheduled Medicines

<table>
<thead>
<tr>
<th>Schedule classification</th>
<th>Access</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unscheduled</td>
<td>No restrictions. E.g. supermarket</td>
<td>Small packet sizes of paracetamol</td>
</tr>
<tr>
<td>Schedule 2</td>
<td>Only sold in a pharmacy</td>
<td>Paracetamol + codeine combination</td>
</tr>
<tr>
<td>Schedule 3</td>
<td>Require consultation with a pharmacist</td>
<td>Topical thrush treatments</td>
</tr>
<tr>
<td>Schedule 4</td>
<td>Require prescription</td>
<td>Blood pressure medications</td>
</tr>
<tr>
<td>Schedule 8</td>
<td>Strict restrictions on storage and supply</td>
<td>Morphine</td>
</tr>
</tbody>
</table>
Drug Names

Chemical Name
- Unique, insight into structure, but complex

Generic (non-proprietary) Name
- Unique name, not trademarked, insight into class

Proprietary / Trade / Brand Name
- Differs between different manufacturers
- Developed by marketing department
Drug Names (Example)

**Chemical Name**
- \((1S,3R,7S,8S,8aR)-8\{2\{2R,4R\}-4\text{-hydroxy-6-oxooxan-2-yl}\text{ethyl}\}-3,7\text{-dimethyl-1,2,3,7,8,8a-hexahydroneaphthalen-1-yl 2,2-dimethylbutanoate}\)

**Generic Name**
- Simvastatin

**Proprietary / Trade / Brand Name**
- Zocor®, Lipex®
## Drug Classifications

<table>
<thead>
<tr>
<th>Broad class</th>
<th>Organ system</th>
<th>e.g. cardiac drugs;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Therapeutic use / pharmacological effect</td>
<td>e.g. anti-hypertensive, diuretic, bronchodilator, inotrope</td>
</tr>
<tr>
<td>Drug class (more specific)</td>
<td>Molecular target and action</td>
<td>e.g. beta 2 adrenergic agonist, ACE inhibitor</td>
</tr>
<tr>
<td></td>
<td>Chemical structure</td>
<td>e.g. β-lactam, thiazide diuretic, benzodiazepine</td>
</tr>
<tr>
<td></td>
<td>Specific site of action</td>
<td>e.g. loop diuretic</td>
</tr>
</tbody>
</table>
## Drug Classes and Names

<table>
<thead>
<tr>
<th>SUFFIX</th>
<th>DRUG GROUP</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>-apine</td>
<td>Atypical antipsychotics</td>
<td>clozapine, olanzapine</td>
</tr>
<tr>
<td>-sartan</td>
<td>Angiotensin-II-receptor antagonist</td>
<td>irbesartan, candesartan</td>
</tr>
<tr>
<td>-azepam</td>
<td>GABA(_A) receptor modulator</td>
<td>diazepam, temazepam</td>
</tr>
<tr>
<td>-coxib</td>
<td>Cyclo-oxgenase-2-inhibitor</td>
<td>celecoxib, rofecoxib</td>
</tr>
<tr>
<td>-dipine</td>
<td>Calcium channel blockers</td>
<td>amlo dipine, nifedipine</td>
</tr>
<tr>
<td>-olol</td>
<td>β-Blockers</td>
<td>metoprolol, propranolol</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitors</td>
<td>omeprazole, pantoprazole</td>
</tr>
<tr>
<td>-pril</td>
<td>ACE inhibitors</td>
<td>perindopril, ramipril</td>
</tr>
<tr>
<td>-statin</td>
<td>HMG-CoA reductase inhibitors</td>
<td>atorvastatin, simvastatin</td>
</tr>
</tbody>
</table>
Drug Formulations

- Oral
- Parenteral
  - Aerosols
  - Topical
  - Suppositories
  - Patches
- Eye drops
Routes of Administration

- Oral or rectal: Gut
- Percutaneous: Skin
- Intravenous: BLOOD
- Intramuscular: Muscle
- Intrathecal: CSF
- Inhalation: Lung

Absorption and distribution:
- Bile through Portal system to Liver and Metabolites
- Kidney: Urine, Faeces, Milk, sweat
- Breast, sweat glands
- Placenta
- Fetus
- Expired air

Elimination
Paramedic Drugs

- Diazepam
- Fentanyl
- Ketamine
- Methoxyflurane
- Midazolam
- Morphine
- Naloxone
- Adrenaline
- Amiodarone
- Atropine
- GTN
- Ondansetron

- Adrenaline
- Ipratropium
- Salbutamol
- Glucagon
- Glucose
- Aspirin
- Benzylpenicillin
Diazepam

• What it is:
  – Benzodiazepine (long acting)

• What it does:
  – Turns on inhibitory pathway in the brain.
  – Sedative, anxiolytic, anticonvulsant, muscle relaxant, and amnesic effects.

• Why paramedics use it:
  – Behavioral emergencies:
    • Sedative.
Midazolam

• What it is:
  – Benzodiazepine (Short acting)

• What it does:
  – Switch on inhibitory pathway in the brain.
  – Sedative, anxiolytic, anticonvulsant, muscle relaxant, and amnesic effects.

• Why paramedics use it:
  – Control of seizures
  – Acute anxiety
Methoxyflurane

• What it is:
  – Analgesic

• What it does:
  – Blocks ion channels involved in the initiation of action potentials.
  – Blocks the transmission of pain response.
  – Reduces pain.

• Why paramedics use it:
  – Initial management of pain.
Morphine

• What it is:
  – Opiate Agonist (Analgesic)

• What it does:
  – Activates μ-opioid receptors.
  – Block the transmission of pain response.
  – Reduces pain.

• Why paramedics use it:
  – Moderate to severe pain that is not controlled by methoxyflurane.
Fentanyl

• What it is:
  – Opiate Agonist (Analgesic)

• What it does:
  – Activates $\mu$-opioid receptors.
  – Blocks the transmission of pain response.
  – Reduces pain.

• Why paramedics use it:
  – Severe pain that is not controlled by morphine or methoxyflurane.
Ketamine

• What it is:
  – NMDA Receptor Antagonist (Analgesic)

• What it does:
  – Blocks flow of ions across the post-synaptic membranes.
  – Causes sedation and reduces pain.

• Why intensive care paramedic use it:
  – Given with morphine in patients with severe pain from trauma.
Naloxone

• What it is:
  – Opiate antagonist

• What it does:
  – Blocks the effects of μ-opioid receptor agonists.

• Why paramedics use it:
  – Opiate agonist overdose:
    • Morphine, heroin, methadone, fentanyl, oxycodone, codeine.
Adenosine

• What it is:
  – Antiarrhythmic (treats dysrhythmia)

• What it does:
  – Slows electrical conduction in the heart (at the AV node).
  – Reduces heart rate.

• Why paramedic use it:
  – ECG diagnosed supraventricular tachycardia (SVT).
Amiodarone

• What it is:
  – Antiarrhythmic (treats dysrhythmia)

• What it does:
  – Slows electrical conduction in the heart.
  – Causes peripheral vasodilation and slows heart rate.

• Why paramedics use it:
  – Unstable ventricular tachycardia.
Adrenaline

• What it is:
  – Adrenergic agonist (Sympathomimetic)

• What it does:
  – Turns on the sympathetic nervous system.
  – ‘Fight or flight response’

• Why paramedics use it:
  – Cardiac arrest (as a component of CPR)
  – Anaphylactic shock
  – Life threatening asthma
Aspirin

• What it is:
  – Antiplatelet

• What it does:
  – Reduces platelet clot formation.

• Why paramedics use it:
  – Chest pain thought to be of cardiac origin.
  – Clinical or ECG evidence of myocardial infarction or ischemia.
Atropine

• What it is:
  – Anticholinergic

• What it does:
  – Stops acetylcholine from binding to muscarinic receptors.
  – Relative increase in sympathetic activity.
  – Increases heart rate.

• Why paramedics use it:
  – Severe symptomatic bradycardia.
Glyceryl Trinitrate

• What it is:
  – Antianginal

• What it does:
  – Reduces oxygen demand by the heart.
  – Improves oxygen supply to the myocardium.

• Why paramedics use it:
  – Acute myocardial infarction
  – Ischemia chest pain (angina)
  – Congestive heart failure
Benzylpenicillin

• What it is:
  – Antibiotic

• What it does:
  – Kills bacterial by blocking bacterial cell wall formation.

• Why paramedics use it:
  – Suspected meningococcal septicaemia.
    • Prevent onset of septic shock.
    • Early (pre-hospital) treatment saves lives.
VENTOLIN® Nebules® 5 mg

Conventional inhalation 5 single dose units of 2.5 mL
Each Nebule contains an isotonic solution of SALBUTAMOL (AS SULPHATE) 5 mg in 2.5 mL
NOT FOR INJECTION
See instruction leaflet before use.
Discard date must be recorded.
Unused Nebules should be discarded three months after opening of the foil.
Store below 30°C. Protect from light.

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BORONIA VICTORIA 3195
Salbutamol

• What it is:
  – Adrenergic agonist (Sympathomimetic)

• What it does:
  – Stimulates adrenergic receptors.
  – Relaxes bronchial smooth muscle.

• Why paramedics use it:
  – Relief of bronchospasm associated with acute asthma or bronchitis.
Ipratropium

• What it is:
  – Anticholinergic (bronchodilator)

• What it does:
  – Blocks acetylcholine receptors in the lungs.
  – Stops bronchoconstriction and mucus secretion.

• Why paramedics use it:
  – Chronic obstructive pulmonary disease.
  – Acute asthma.
Glucose

• What it is:
  – Anti-hypoglycaemic

• What it does:
  – Directly increases the amount of glucose in the blood.
    • Serves as key fuel source in the body.
    • Main fuel source utilised by the brain.

• Why paramedics use it:
  – Hypoglycaemia
Glucagon

• **What it is:**
  – Anti-hypoglycaemic

• **What it does:**
  – Indirectly increases the amount of glucose in the blood.

• **Why paramedics use it:**
  – Persistent hypoglycemia that doesn’t respond to administration of glucose.