BIOP211

Session 1

Pharmacology

Department of Bioscience

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Session Outline

- Introduction to pharmacology
- Drug nomenclature, Over-the-counter (OTC) and complementary medicines, CM
- Legal and ethical considerations
- Scheduling
- Drug studies and risk management
- Pharmacodynamics
- Pharmacokinetics
Pharmacology

- **Pharmacology**
  Study of drugs (legal and illegal, OTC and prescription medications, natural and synthetic chemicals) including their actions and effects (both beneficial or potentially toxic) in living systems/tissues

- **Pharmacognosy**
  The isolation and characterisation of drugs from natural sources i.e plants, microbes, animal tissues, minerals
Naming Drugs

- There are a number of different ways to classify drugs:
  - OTC / Prescription / CM
  - Schedule / safety in pregnancy
  - Therapeutic class – based on the body system they affect
- Chemical names – generally long and complicated
- Generic – official Australian Approved Name (easier and shorter than the chemical name)
- Brand Name – different for different company or formulation
Drug Names and Classes

Drug names (example antibacterial antibiotic – amoxycillin)

- Chemical: D(-)-α-amino-p-hydroxybenzylpenicillin
  - Description of chemical composition & molecular structure
- Generic/non-proprietary: amoxycillin
  - Official drug name (AAN – Australian approved name) assigned by manufacturer with approval from local drug regulating authority
- Proprietary (brand or trade): Alphamox®, Amohexal®, Amoxil®
  - Copyright for marketing purposes, restricting use of name to individual drug company & referring to particular formulation of drug
Therapeutic Classes

Drugs are classified in therapeutic classes and sub-classes depending on their main indications and body system in which they act.

Eg: Alimentary System

- a) hyperacidity, reflux and ulcers
- b) antispasmodics, motility agents
- c) laxatives
- d) antidiarrhoeals
- e) digestive supplements and cholelitholytics
- f) topical anorectal medications
Over the Counter Medication (OTC)

- Over the counter medication (OTC)
  - bought by the public to self treat minor illnesses
  - approx 60% of all purchased medication is OTC

- Characteristics of OTC drugs
  - Indicated for conditions that are generally mild or self-limiting
  - Generally considered safe and effective for self treatment with a low incidence of severe adverse effects and low potential for harm
  - Assumes the drug is made according to good manufacturing practice (GMP) and that the consumer follows the directions on the label
  - Show good efficacy for minor symptoms across a wide population group
OTC Categories

- Analgesics
- Antacids
- Laxatives
- Anti-diarrhoeal
- Cough-cold preparations
- Antihistamines
- Nutritional supplements
Potential Problems with OTC Drugs

- Self diagnosis
- Adverse effects and drug interactions
- Labelling
- Drug marketing and Therapeutics Good Administration (TGA)
- Potency and Efficacy
- Combinations of products
- Consumers must obviously be educated to reduce the risk of adverse events
Legal and Ethical Considerations

- In Australia, therapeutic goods including drugs are controlled by Commonwealth, state and territory laws.
- Drug regulation by the Therapeutic Goods Admin (TGA):

  **TGA is an** Australian Register of Therapeutic Goods, for:
  1. Registered medicines (Prescription - high risk; Non-prescription low risk);
  2. Listed medicines (Most OTC medicines);

  **TGA: Drugs used for medicinal purposes in humans (registered, non-prescription, listed e.g. OTC and complementary medicines)**

  **Prohibited drugs**

  **Primary aims:** Control the supply of drugs prone to abuse;

  Regulate the availability of substances for therapeutic use;

  Include certain products on the Pharmaceutical Benefits Scheme (PBS)
New Drug Investigations

- TGA uses international standards for Clinical Safety Data Management and reporting. Sponsor must register the trial with TGA, Clinical trial exemption or notification scheme.
- Ethics committee approval of Randomized controlled clinical trials (RCCT) & other clinical trials.
- Animal studies or high throughput screening tests, knowledge applied to risk assessment.
- Pharmacokinetics and pharmacodynamics applied to risk assessment (risks vs benefits).
- Randomized controlled clinical trials (RCCT) to test efficacy and investigate likely hazards.
- Then post-marketing studies (pharmacovigilance) once medicine / device approved for registration with TGA.
Stages of Drug Development

**Drug Discovery**
- Target selection
- Lead-finding
- Lead optimisation
- Pharmacological profiling

**Preclinical Development**
- Pharmacokinetics
- Short-term toxicology
- Formulation
- Synthesis scale-up

**Clinical Development**
- **Phase I**
  - Pharmacokinetics, tolerability, side-effects in healthy volunteers
- **Phase II**
  - Small-scale trials in patients to assess efficacy & dosage
  - Long-term toxicology studies
- **Phase III**
  - Large-scale controlled clinical trials

**Regulatory Approval**
- Submission of full data and review by regulatory agencies
- Postmarketing surveillance

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Drugs candidate, Development compound, Regulatory submission, Drug approved for marketing

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Classifications of ADR and ADE:

Adverse drug reactions (ADR) and events (ADE) are classified as:

i) Type A - Augmented or predictable

ii) Type B - Bizarre or Unpredictable/idiosyncratic [drug allergy or hypersensitivity]

iii) Type C - Chronic; reactions that develop with long-term therapy [development of drug tolerance and physical dependence]

iv) Type D - Delayed effects such as carcinogenicity or teratogenicity [delayed fertility]

v) Type E - End of use; reactions after stopping (withdrawal)

vi) Type F - Failure of therapy (e.g. St John’s Wort and oral contraceptive pill)

Adverse drug reactions and events are reported to the TGA for

1. Registered medicines
2. Listed medicines (Most OTC medicines);
3. Complementary medicines
# Mechanisms of Toxicology - Carcinogenicity

Table 22.9 Some Chemical and Environmental Carcinogens

<table>
<thead>
<tr>
<th>Carcinogen</th>
<th>Tumor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestos</td>
<td>Lung, respiratory tract</td>
</tr>
<tr>
<td>Arsenic</td>
<td>Skin, lung</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Prostate, kidneys</td>
</tr>
<tr>
<td>Chromium</td>
<td>Lung</td>
</tr>
<tr>
<td>Nickel</td>
<td>Lung, sinuses</td>
</tr>
<tr>
<td>Aflatoxin</td>
<td>Liver</td>
</tr>
<tr>
<td>Nitrites</td>
<td>Stomach</td>
</tr>
<tr>
<td>Aniline dyes</td>
<td>Bladder</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Liver</td>
</tr>
</tbody>
</table>

Timberlake, *General, Organic, and Biological Chemistry*. Copyright © Pearson Education Inc., publishing as Benjamin Cummings
Mutagenesis vs Oncogenesis vs Carcinogenesis

- **Mutagenesis** – processes on exposure to a mutagen.
- **Carcinogenesis** – processors which may be synergistic agents are initiators and/or promoters.
- **Oncogenesis** – processes which involve proto-oncogenes changing to oncogenes as the cells transform to malignant cells.
Apoptosis (programmed cell death) vs necrosis

- In apoptosis, DNA and cell contents are metabolised e.g. purine metabolism to **uric acid**, for excretion.
- In necrosis, there is loss of cell contents including DNA. **NO (g) radical** mediates necrotic processes.

Fig 3-25 Stages of Necrosis: pyknosis, karyolysis (Huether & McCance, 2006)

Fig 6_13 Mechanisms of apoptosis (Huether and McCance, 2006)
Teratogenicity e.g. thalidomide

- Thalidomide and lenalidomide induce apoptosis, have immunosuppressant and anti-inflammatory actions but are category X in Pregnancy teratogenic (see population data, 1958 to 1962)

- Current, registered indications for thalidomide and lenalidomide include some cancer treatments and thalidomide is immunomodulatory in a rare skin condition
Mechanisms of Toxicity – ADR type D

- Cancer & damage to the foetus that is seen later in the lifespan would be ADR type D (delayed effects)

- E.g. Female offspring of women who received stilbestrol during pregnancy had an increased risk of vaginal cancer (ADR type D, delayed effect)
Drug Schedules

- The keystone to scheduling is the potential for toxicity. All medicines are inherently toxic and can cause harm.
- The degree of potential toxicity (i.e. risk to safety) determines the schedule under which a drug is classified.
- Scheduling in Australia is legally a State matter, but all adhere to the Poisons Standard. The Poisons Standard is the legal title of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).
- Changes to Drug scheduling is on application to Medicines and Poisons Scheduling Secretariat (http://tga.gov.au/industry/scheduling-forms-poisons-standard-amend.htm)
Schedules

- S1 – not currently in use
- S2 – PHARMACY MEDICINE
- S3 – PHARMACIST ONLY MEDICINE
- S4 – PRESCRIPTION ONLY MEDICINE
- S5 – CAUTION, readily available but require caution in handling, storage and use
- S6 – POISON, available but more hazardous/poisonous than S5
- S7 – DANGEROUS POISON, special precautions or individual regulations
- S8 – CONTROLLED DRUG, legitimate therapeutic uses but have addictive or abuse potential
- S9 – PROHIBITED SUBSTANCES, drugs of abuse, prohibited by law except for approved research purposes by the Governor
The relationship between dose of a drug and the utility of that drug in treating the patient is described by two basic areas of pharmacology:

- **Pharmacodynamics** - ‘How/What the drug does to the body’ – Includes physiological and biochemical effects of drug, mechanisms of action, effect of drugs on receptors, possible adverse reactions

- **Pharmacokinetics** – ‘What the body does to the drug’ – How the drug is altered as it moves through the body (absorption, distribution, metabolism, excretion)
Phases Affecting Drug Activity

- There are three key phases that will affect drug activity
  - Pharmaceutical phase
  - Pharmacodynamic phase
  - Pharmacokinetic phase
Pharmaceutical Phase

- Drug is administered in a given type of formulation or dosage form
- Disintegrates into smaller particles
- Leads to dissolution of drug
- Drug ready for absorption
- The more rapid the rate of dissolution the more rapid the drug is presented to the membrane for absorption
- Rate of absorption is as follows:
  - liquids > suspensions > powders > capsules > tablets > coated tablets > EC tablets
Pharmacodynamic Phase

- Study of the interaction between a drug and its molecular target and of the pharmacological response – Mechanism of action
- ‘What the drug does to the body
- Ideally, drugs would show complete specificity for a required molecular binding site
  - One target
  - One site of action
  - One effect
Molecular Targets for Drugs

- Drugs act on four main types of protein targets:
  - Carriers
  - Enzymes
  - Ion channels
  - Receptors

- When drugs bind to these targets, they can inhibit their natural action, increase their natural action, or somehow alter the biochemistry of the cell/tissue/body by interacting with the target
Carriers (Transporters)

- Ions and small molecules that lack lipid solubility, need to be transported via carriers across biological membranes.

Examples:
- Glucose, sodium, calcium transported in and out of cells.
- Involved in the uptake of chemicals acting at nerve terminals (noradrenaline, 5-HydroxyTryptamine (5-HT) and glutamate).

- Drugs binding to carrier proteins can inhibit the movement of the natural substrate.

- Other drugs may utilise the transporters to enter target cells.

- Some drugs may keep gated carriers permanently open.
Enzymes

- Biological catalysts that control biochemical reactions of the cells.
- Drugs can inhibit the action of a specific enzyme which will alter the physiological response.
- Drug may be designed to closely resemble an enzyme substrate so that the enzyme combines with the drug instead of the substrate.
  - May lead to the accumulation or use of an abnormal substrate.
  - May be used to activate a prodrug into the drug.
Inhibition of enzymatic activity – cyclooxygenase, COX

NORMAL

Cell Membrane → ARACHIDONIC ACID

PATHOLOGICAL e.g. bacteria insult

Cell Membrane → ARACHIDONIC ACID

ARACHIDONIC ACID → CYCLOOXYGENASE

CYCLOOXYGENASE → PROSTAGLANDINS

PROSTAGLANDINS → Pain, Fever

BACTERIAL INFECTION
Inhibition of enzymatic activity – COX inhibitors

Paracetamol

- Mechanism of Action: Cyclooxygenase (COX) inhibitor
- Actions: Decreases levels of Prostaglandins
- Therapeutic effect: Reduces pain and fever
Ion Channels

- Cell membranes regulate the flow of ions and metabolites through ion channels.
- This maintains an electrochemical gradient (interior vs exterior of the cell).
- Drugs can be used to block these channels, or modify their rate of opening/closing if gated.

[Diagram of ion channels: Open ion channel and Blocked ion channel]
Receptors

- One of the most important targets for drug therapies
- Refers to cellular macromolecules in chemical signalling between and within cells
- A certain portion of a drug molecule binds to a receptor site to produce a pharmacological effect (shows structural specificity) – (drug blocks or activates receptor)
- Agonist activates receptor
- Antagonist blocks the receptor

(Thibodeau and Patton, 2006)
Families of Receptors

1. **Ligand-gated ion channels** – e.g. nicotinic acetylcholine receptor, type A gamma-aminobutyric acid (GABA$_A$); located in cell membrane

2. **G-protein-coupled receptors and 2$^{nd}$ messengers**; located in cell membrane; e.g. too numerous endogenous substances to mention. One-third of all marketed drugs may target GPCR (Robas et al, 2003)

3. **Kinase-linked receptors**; located in cell membrane e.g. insulin (and other non-steroid hormones)

4. **Nuclear receptors**; located in the cytosol e.g. hydrocortisone (steroid hormone)
GPCR and 2\textsuperscript{nd} Messenger

- G-protein coupled receptors
- Important site of drug action affecting smooth muscle, secretory cells
Nuclear Receptors

- Regulate nuclear transcription
- Endogenous regulatory ligand binds to intracellular receptors
- First step in cell signalling leading to the production of proteins
- Long time course

Fig. 16-8. Steroid hormone mechanism. According to the mobile-receptor model, lipid-soluble steroid hormone molecules detach from a carrier protein (1) and pass through the plasma membrane (2). The hormone molecules then pass into the nucleus where they bind with a mobile receptor to form a hormone-receptor complex (3). This complex then binds to a specific site on a DNA molecule (4), triggering transcription of the genetic information encoded there (5). The resulting mRNA molecule moves to the cytosol, where it associates with a ribosome, initiating synthesis of a new protein (6). This new protein—usually an enzyme or channel protein—produces specific effects in the target cell (7). Some steroid hormones also have additional secondary effects such as influencing signal transduction pathways at the plasma membrane.
Nuclear Receptors - hydrocortisone

H = hydrocortisone hormone
(Endogenous substance)
Exogenous substance e.g. steroid drug such as beclomethasone (Rx in asthma)

(Huether and McCance, 2008)
Pharmacokinetics

- What the body does to the drug?
- In order for a drug to exert an effect, it must reach its site of action.
- Concentration of drug at the site of action is affected by:
  - Absorption
  - Distribution
  - Metabolism
  - Excretion
Desensitisation of Receptors

- Refers to a decrease in the response of the receptor-second messenger system
- Downregulation
  - Decrease in receptor number → desensitisation and ↓ response
- Upregulation
  - Increase in receptor number → receptor super-sensitivity
- Turnover of receptors
- Tachyphylaxis = repeated exposure to drug, initial response cannot be reproduced, even with larger doses e.g. Transdermal nitroglycerin
- Can explain ADR type E – end of use responses and effects
Examples of New Drug Developments, endogenous mediators

- Endogenous mediators acting at receptors, enzymes, new drug investigations
- Mediators – organic endogenous compounds – hormones, local hormones, neuromodulators
- Examples:
  - 5-hydroxytryptamine (5-HT or serotonin) agonists and antagonists (Phase IV)
  - Purines affecting clotting and acting as neuromodulators (Pre-clinical)
  - Cannabinoids (anandamide endogenous cannabinoid); tetrahydrocannabinol, THC, may work synergistically with opioids. Receptors recently characterised. Pre-clinical trials in Australia (?)

• Peptides as mediators. E.g. endothelin which affects nitrogen monoxide synthesis, Phase IV and some Phase III. Bosenten, darosenten, generic names reflect mode of action as antagonists at endothelin receptors

• Endogenous free radicals: Nitric oxide, (nitrogen monoxide, NO, transported by Haemoglobin, vasodilator, releases endogenous nitrates)
Bliss in your Brain

Acupuncture works at the receptors for the human, natural cannabinoid called anandamide (bliss). Complementary medicine studies into the use of herbal remedies at the recently characterised CB1 and CB2 receptors for cannabis.

Bliss receptors for arachindonyl-ethanolamide, anandamide, the endogenous cannabinoid (Badgaiyan, 2010, p. 1174; Shou, Y et al, 2013; Wiley, 2010)

Endogenous Mediators - neurotransmitters

Review:

- ACh – acetylcholine at muscarinic and nicotinic receptors.
- NA - Noradrenaline NA at alpha α and β receptors (norepinephrine (Tortora & Derrickson, 2014, p. 233)
- 5-HT – 5-hydroxytryptamine – serotonin and D - dopamine
- Nitrogen monoxide (nitric oxide) NO(g)
Summary: What ways do drugs act?

- Revision Tutorial 1.3.1 Activity 🌱 Pharmacodynamics:
  - Block or increase movement of compounds (ions neurotransmitters)
  - Enzyme inhibition or modification
  - Affect receptors (four types of receptors: GPCR & 2\textsuperscript{nd} messenger, kinase linked receptors, ligand-gated ion channels, nuclear receptor in the cytoplasm)

- What the body does to the drug/ what the drug does to the body? Pharmacokinetics/Pharmacodynamics?

- Current issues in health and healing (Goldacre, 2010; Jeff, Snyder and Myers, 2006) 📜 📝
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