Pharmacology is derived from a Greek word (pharmakon). The Greeks used this word to mean a medicine, a poison or a magic spell.

Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose. The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V). The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).
Objectives

- Be familiar with the principal diseases of the respiratory system and the common medicines used to treat respiratory disease
- Learn the mechanism of action, clinical benefits and adverse effects of common medicines

Lectures are intended to highlight main mechanisms of disease and actions of common medicines. Disease and pharmacological mechanisms can often be found on Wikipedia. Adverse effects are often complex and may relate to interaction of several medicines used at the same time. Consult MedSafe (http://www.medsafe.govt.nz/) or NZ Formulary (http://nzformulary.org/) for details.

Respiratory Diseases

- Asthma & Allergic Rhinitis
- Upper respiratory tract infection (URTI)
- Coughs and colds
- Chronic Obstructive Pulmonary Disease (COPD)
- Cystic fibrosis

What are the principal respiratory diseases that are treated with medicines?
Malignant diseases such as lung and throat cancer and antibacterial/antiviral/antifungal treatment of respiratory tract infections are not covered in this lecture.
Allergic Disease

- Asthma ("wheeze") and allergic rhinitis ("hay fever")
  - Caused by allergy to inhaled antigens
    - e.g. pollen, house dust mite
  - Typically reversible without treatment
  - Medicines are largely symptomatic
Coughs and Colds

Sore Throats

- Symptoms of allergy and/or infection
- Usually viral infection
  - Choryza – the common cold
  - Influenza
  - Infectious mononucleosis – glandular fever
- No proven place for use of medicines
  - Exception – Streptococcal infection

Common symptoms. Mainly self limiting. Vitamin C use is controversial. A profitable placebo for pharmacists?

Limited benefit of anti-virals (e.g. oseltamivir (Tamiflu)) in influenza.

“A 2014 Cochrane review concluded that oseltamivir does not reduce hospitalizations, and that there is no evidence of reduction in complications of influenza”

Cough cures?

Medicines have little objective benefit. Symptomatic remedies (steam inhalation, hot shower, whisky etc)

Penicillin to reduce risk of rheumatic fever
Airway obstruction treatments are much the same for asthma and COPD.

Acute exacerbations can be difficult to distinguish from asthma and heart failure. Progressive disease. No medicines known to slow progression of obstructive features. Late stage disease may require domiciliary oxygen. Mucolytics have little objective benefit. Mainly placebo effect.

https://en.wikipedia.org/wiki/Mucokinetics: "Many mucokinetic drugs are available, including Sodium citrate or Potassium citrate, Potassium iodide, Guaiaphenesin, Tolu balsam, Vasaka, Ammonium chloride. Many mucolytic drugs are available, including acetylcysteine, ambroxol, carbocisteine, erdosteine, mecysteine, and dornase alfa".

https://en.wikipedia.org/wiki/Cystic_fibrosis: "cystic fibrosis transmembrane conductance regulator protein (CFTR)" "CFTR is involved in production of sweat, digestivefluids, and mucus. When CFTR is not functional, secretions which are usually thin instead become thick."

Many clinical teams (respiratory, gastrointestinal, nutritional, psychological). Multiple medicines. Lots of potential interactions. Challenge for everyone to stay alert to medicine interactions and adverse effects.
**Allergy Mechanism**

- **Inflammation**
  - Swelling
  - Itching
  - Liquid exudate

- **Mediators**
  - Mast cells
  - Eosinophils
  - Histamine
  - Cytokines

**Allergy Treatment**

- **Bronchodilators (asthma, COPD)**
  - salbutamol, tiotropium
  - theophylline, magnesium sulphate (hospital)

- **Anti-inflammatory steroids (asthma)**
  - beclomethasone, prednisone

- **Mast cell stabilizer/leukotriene receptor antagonist (asthma)**
  - cromoglicate, montelukast

- **Antihistamine (hay fever)**
  - fexofenadine

- **Vasoconstrictor (hay fever, croup)**
  - oxymetazoline, nebulized adrenaline (pseudoephedrine, cocaine)

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Bronchodilators are generally rapid in onset "relievers"

Anti-inflammatory steroids are generally slow in onset "preventers"

https://en.wikipedia.org/wiki/Cromoglicic_acid

"cromolyn sodium. This drug prevents the release of inflammatory chemicals such as histamine from mast cells."

https://en.wikipedia.org/wiki/Montelukast

"It blocks the action of leukotriene D4 (and secondary ligands LTC4 and LTE4) on the cysteiny1 leukotriene receptor CysLT1 in the lungs and bronchial tubes by binding to it. This reduces the bronchoconstriction otherwise caused by the leukotriene and results in less inflammation."

Antihistamines are not used to treat asthma because they have no effect on bronchoconstriction.

Fexofenadine (non-sedating H1-histamine receptor antagonist) is effective by suppressing histamine induced acute irritation and exudation.

Vasoconstrictors reduce exudate by reversing inflammatory cytokine and histamine induced vasodilation.

http://nzf.org.nz/nzf_6107

"Symptoms of nasal congestion associated with the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays. These all contain sympathomimetic drugs which exert their effect by vasoconstriction of the mucosal blood vessels which in turn reduces oedema of the nasal mucosa. They often give rise to rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilatation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events."
Mechanism

- Beta2-adrenoceptor agonists
  - salbutamol (short acting beta agonist)
  - salmeterol (long acting beta agonist; LABA)
  - activate beta-receptors which leads to bronchial smooth muscle relaxation

- Muscarinic cholinergic antagonists
  - Iprotropium, tiotropium (LAMA)
  - Block acetyl choline (bronchoconstrictor)

Long acting beta agonists (LABA) have high affinity for receptor and partition into cell membrane near receptor. Long action may due to slow dissociation from receptor and/or deport slow release from membrane to receptor. LABAs (salmeterol, formoterol) only in severe asthma (see NZ formulary http://nzf.org.nz/nzf_1706#nzf_1710) Olopatadine is an ultra-long-acting β adrenoceptor agonist (ultra-LABA) used as an inhalation for treating patients with chronic obstructive pulmonary disease (COPD), manufactured by Boehringer Ingelheim. https://en.wikipedia.org/wiki/Olodaterol

LAMA=long acting muscarinic agonist
Treatment & Mechanism

- Anti-inflammatory Steroids
  - Inhaled (topical)
    - Beclomethasone
  - Systemic (oral)
    - Prednisone (or prednisolone)

- Intra-cellular glucocorticoid receptor
  - Slow turnover of proteins which lead to release of inflammatory cytokines
  - Slow onset of action and persistent effect

Theophylline Target Concentration

Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomised Concentration-Controlled Trial

Nicholas Holford, Peter Black, Ron Couch, Julia Kennedy and Robin Brian

- How can a target concentration of 10 mg/L be maintained?

Clearance

Clearance describes the relationship between concentration and the rate of elimination of drug from the body

\[ \text{Rate Out} = \text{CL} \times \text{Concentration} \]
Maintenance Dose Rate

- At Steady State:
  
  \[ \text{Rate Out} = \text{Rate In} \]

- Therefore

  \[ \text{Rate Out} = CL \cdot \text{Concentration} \]
  
  \[ mg/h = L/h \cdot mg/L \]
  
  \[ 30 mg/h = 3 L/h \cdot 10 mg/L \]

Adverse Effects

- Beta agonists
  » Tachycardia, tremor
  » Arrhythmias, hypokalaemia

- Steroids
  » Acute courses – very few adverse effects
  » Mouth/throat infection (“thrush”)
  » Growth slowing (children)

- Theophylline
  » Nausea (vomiting)
  » Tachycardia (arrhythmias – heart, brain)

Pulmonary Toxicity of Medicines and Poisons

- Pulmonary Fibrosis
  » Amiodarone (anti-arrhythmic)
  » Nitrofurantoin (antibiotic)
  » [Methysergide (anti-migraine)]
  » Paraquat (weed killer)

Maintenance dose rate can be predicted if the target concentration and the drug clearance are known. Steady state drug concentrations are maintained when the rate of drug administration (rate in) is equal to the rate of elimination (rate out). Using the definition of clearance we can predict the steady state rate in. Note the units of clearance are typically L/h and concentration is mg/L. Maintenance dose rates are then readily predicted with units of mg/h.

Adverse Effects

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https://en.wikipedia.org/wiki/Methysergide
https://en.wikipedia.org/wiki/Paraquat
https://en.wikipedia.org/wiki/Pulmonary_toxicity
Monitoring Treatment

- Asthma
  - Peak Expiratory Flow Rate meter
  - Patient symptom diary
  - Theophylline target concentration intervention
    - NZ formulary out of date and misleading
    - Target is 10 mg/L (55 umol/L)
    - Sample in middle of dosing interval

http://nzf.org.nz/nzf_1756

“The therapeutic drug monitoring plasma-theophylline concentration for optimum response 55–110 micromol/litre (10–20 mg/litre); measure theophylline concentration 4–6 hours after a dose (sampling times may vary—consult local guidelines), and at least 5 days after starting oral treatment, and at least 3 days after any dose adjustment. There is no point in waiting 5 days after starting treatment. Steady state is typically reached after 2 days. Blood sampling in the middle of the dosing interval is closest to steady state average conc and thus most useful for estimating clearance.”

The way to go!