Respiratory Pharmacology

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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

Respiratory Diseases

➢ Asthma & Allergic Rhinitis

➢ Upper respiratory tract infection (URTI)

➢ Coughs and colds

➢ Chronic Obstructive Pulmonary Disease (COPD)

➢ Cystic fibrosis

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.

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 (A, B, C, D)
  - Covid-19 (SARS-CoV-2)
  - Infectious mononucleosis – glandular fever
- No proven place for use of medicines
  - Exception – Streptococcal infection


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

Vitamin C use is controversial. A profitable placebo for pharmacists?

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

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

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

Claims of benefit of chloroquine to treat covid19 associated pneumonia have been made (Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. BioScience Trends. 2020;DOI: 10.5582/bst.2020.01047.) but no reports have been published describing clinical trials and results (1 March 2020).

Cough cures?

http://www.webmd.com/cold-and-flu/features/cough-relief-how-lose-bad-cough#1

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

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

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, Guaiphenesin, Tolu balsam, Vasaka, Ammonium chloride. Many mucolytic drugs are available, including acetylcysteine, ambroxol, carbocisteine, erdosteine, mecysteine, and domae alfa.”
Cystic Fibrosis

- Genetic cause
  - 1 in 3000 newborns affected
  - CFTR - cystic fibrosis transmembrane conductance regulator protein

- Symptoms may start in infancy
  - Respiratory (frequent infections)
  - Intestinal (malabsorption)

- Lifelong management

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Allergy Mechanism

- Inflammation
  - Swelling
  - Itching
  - Liquid exudate

- Mediators
  - Mast cells
  - Eosinophils
  - Histamine
  - Cytokines

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Allergy Treatment

- Bronchodilators (asthma, COPD)
  - formoterol, 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”
Short acting beta agonists (SABA) are no longer recommended
Anti-inflammatory steroids are generally slow in onset “preventers”
Cromolyn sodium. This drug prevents the release of inflammatory chemicals such as histamine from mast cells.
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 vasodilatation. 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 vasodilation 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.”

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**Bronchodilator Mechanism**

- Beta2-adrenoceptor agonists
  - salbutamol (short acting beta agonist)
  - formoterol, 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)
- Theophylline
  - Adenosine receptor antagonist (like caffeine)
  - Phosphodiesterase inhibitor

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. NZF recommends LABAs (salmeterol, formoterol) only in combination with inhaled steroids (see NZ formulary http://nzf.org.nz/nzf_1706#nzf_1710).


Olodaterol is an ultra-long-acting beta adrenoreceptor 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
The FEV1 is a measure of airway resistance. Tiotropium is an inhaled anti-cholinergic bronchodilator. FEV1 was measured before and after bronchodilatation with inhaled salbutamol (albuterol). Patients with chronic obstructive pulmonary disease (COPD) treated with placebo or with tiotropium show an initial symptomatic response which appears to be maintained in the tiotropium treated group. There is no indication of a disease modifying effect. Before bronchodilatation, the annual rates of decline were the same in the tiotropium group and the placebo group: 30±1 ml per year. After bronchodilatation, the annual rate of decline was 40±1 ml per year in the tiotropium group, as compared with 42±1 ml per year in the placebo group. Note the much bigger response to beta-agonist bronchodilator than to tiotropium.


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

https://en.wikipedia.org/wiki/Glucocorticoid_receptor
Prednisone has short half-life (2-4 h). Doses given once a day or event alternate days. Prednisone and prednisolone are interconvertible in the body. No real differences in the clinical pharmacology of these 2 molecules. https://en.wikipedia.org/wiki/Prednisone
PKPD of inhaled corticosteroids http://www.atsjournals.org/doi/full/10.1513/pats.200403-025MS
Theophylline Target Concentration

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

A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting. If the target concentration is known what dose rate is needed to maintain the concentration at the target?

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

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

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

- **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)

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

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The way to go!