Drugs used in Asthma and COPD

Dr Andrew Smith
Outline

• Modes of Delivery

• Overview of the drugs used in Asthma and COPD
  • β-Agonists
  • Anti-Muscarinics
  • Xanthines
  • Corticosteroids
  • Leukotriene Receptor Antagonists
  • Monoclonal Antibodies
  • Others inc. LTOT
  • Pregnancy and Breastfeeding

• Summary

• Treatment Regimens:
  • Long-term management of Asthma
  • Acute Exacerbation of Asthma
  • Long-term Management of COPD
  • Acute Exacerbation of COPD
Modes of Delivery

- Oral
- Inhalers:
  - **Metered dose** – the standard inhaler. Fixed amount of aerosol drug is administered.
  - **Breath-activated** (may still be pressurised, or dry powder). Easier to use. Examples are the Accuhaler or Turbohaler.
  - **Spacers** can be used to help increase drug delivery.
  - **Inhaler Technique:** [www.asthma.org.uk/Sites/healthcare-professionals/pages/inhaler-demos](http://www.asthma.org.uk/Sites/healthcare-professionals/pages/inhaler-demos)
- **Nebulisers** – air or oxygen is driven through liquid drug via face mask.
- Intravenous
β2-Agonists

• Act directly on smooth muscle causing bronchodilation.
  • “Beta-adrenergic receptors are coupled to stimulatory G proteins which activate adenyllyl cyclase, which catalyzes the production of cAMP. In the lung, cAMP causes a decrease in the intracellular calcium concentration and, via activation of protein kinase A, both inactivates myosin light chain kinase and activates myosin light chain phosphatase. In addition, beta-2 agonists open large conductance calcium-activated potassium channels. The combination of decreased intracellular calcium, increased membrane potassium conductance, and decreased myosin light chain kinase activity leads to smooth muscle relaxation and bronchodilation.”
  • In short: β2-agonist ➔ Raised cAMP ➔ Decreased Ca^{2+} ➔ Bronchodilatation
• Have a rapid onset of action so can be used symptomatically or before exercise.
• Long acting versions are used when preventative therapy is required.
• Used in both asthma and COPD. Also as a tocolytic in obstetrics
• Limited benefit in infants due to minimal β-receptors in the lungs.
β2-Agonists

Short acting (3-5 hours) – *INH, NEB, PO, SC, IM and/or IV*
- Salbutamol – Inh 100-200µg qds, Neb 2.5-5mg, IV from 5µg/min
- Terbutaline – Inh 500µg qds, Neb 5-10mg, IV from 90µg/min

Long Acting (12 hours) – *Inhaled only*
- Salmeterol – 50-100µg bd
- Formoterol – 12µg bd

Side-effects
Fine tremor, muscle cramps, nervous tension, palpitations, tachycardia, sleep disturbance, hypokalaemia (a therapeutic aim in some situations)
Paroxysmal bronchospasm can occur.
Anti-Muscarinics

• Cause bronchodilation and reduce mucus secretion by blocking muscarinic acetylcholine receptors in the lung which promotes the degradation of cGMP.
• They have longer action and greater bronchodilator effect than the β2 agonists.
• Used in both asthma and COPD.

Short Acting – *Inhalation and nebulised*
  • Ipratropium Bromide – Neb 250-500mcg, INH 20-40mcg

Long Acting - *Inhaled only*
  • Tiotropium – 18mcg

Side Effects
• Dry mouth, nausea, constipation. Caution in those with bladder outlet obstruction and glaucoma.
Methylxanthines

Types:
• Theophylline – given PO
• Aminophylline (more soluble) – given PO or IV

• A loading dose is required for the xanthine-naive

• They act as a:
  • *Phosphodiesterase inhibitor* – raising cAMP and therefore bronchodilation
  • *Adenosine receptor blocker* – causing bronchodilation
  • *Histone deacetylase activator* – suppressing genes involved in inflammation.

• Primarily used in acute/chronic asthma. There is still debate for its use in COPD.
Methylxanthines

- The therapeutic range is narrow (10-20mg/L). Plasma level monitoring is therefore required.
- It is metabolised in the liver by cytochrome P450 so its concentration is affected by liver disease and enzyme inhibitors/inducers.

Side effects
- Gastro – Nausea, vomiting, gastric irritation, diarrhoea
- Cardiac – palpitations, tachycardia, arrhythmias (mainly due to its effect on adenosine)
- CNS – headache, insomnia, convulsions
Summary of β-agonists, Anti-Muscarinics and Theophylline

AC: Adenylate Cyclase
PDE: Phosphodiesterase
(c)AMP: (cyclic) Adenosine Monophosphate
Corticosteroids

• Used in the prevention and acute management of both asthma and COPD. In COPD, their preventative use should be assessed by a steroid trial.

• “The anti-inflammatory effects are mediated either by direct binding of the glucocorticoid/glucocorticoid receptor complex to glucocorticoid responsive elements in the promoter region of genes, or by an interaction of this complex with other transcription factors, altering gene transcription.

• Glucocorticoids inhibit many inflammation-associated molecules such as cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules. They also up-regulate anti-inflammatory molecules”

• All in all, they reduce inflammation, oedema and secretions.
Corticosteroids

Can be given by numerous routes:

**Inhaled**
- Beclometasone – 200-400 μg bd, up to 800μg bd
- Budenoside – 100-800 μg bd

**Oral**
- Prednisolone – 30-60mg od

**IV**
- Hydrocortisone – 100-200mg

**Note,** oral and IV steroids have the same benefit in the acute setting (presuming the patient can swallow and isn’t vomiting)

**Inhaled Side-effects**
- Inhaled steroids have lowered systemic absorption but systemic effects can occur; especially with long use and high doses.
- Furthermore, inhaled steroids can increase oral thrush and lower respiratory tract infections (advise the patient to wash mouth out after use)
Corticosteroids – Systemic Side Effects!

- Emotional disturbance
- Enlarged sella turcica
- Moon facies
- Osteoporosis
- Cardiac hypertrophy (hypertension)
- Buffalo hump
- Obesity
- Adrenal tumor or hyperplasia
- Thin, wrinkled skin
- Abdominal striae
- Amenorrhea
- Muscle weakness
- Purpura
- Skin ulcers (poor wound healing)

**Endocrine:** HPA suppression, hyperglycemia

**Musculoskeletal:** growth retardation, skeletal-muscle myopathy, osteoporosis/fractures, aseptic necrosis of bone, subcutaneous tissue atrophy

**Central nervous system:** psychiatric disturbances, pseudotumor cerebri

**Immune system:** impaired wound healing, leukocyte and monocyte inhibition

**Fluid/electrolyte balance:** sodium and water retention, hypokalemia

**Cardiovascular:** hypertension

**Ophthalmologic:** glaucoma, posterior subcapsular cataracts

**Other:** pancreatitis, skin striae, moon facies, central redistribution of fat
Leukotriene Receptor Antagonists — e.g. Montelukast

- Block the effects of cysteinylic leukotrienes which are related to mast cell and eosinophil bronchoconstriction and inflammation.

- Of benefit in aspirin and exercise induced asthma.
Leukotriene Receptor Antagonists

Types
• Montelukast – 10mg in the evening PO
• Zafirlukast – 20mg bd PO

Side-effects
• Gastrointestinal disturbances, headache, insomnia, arthralgia, myalgia, bleeding disorders.
• Rare reports of Churg-Strauss syndrome, especially when corticosteroids are reduced. Be aware of eosinophilia, vasculitic rash and worsening pulmonary symptoms.
Anti-IgE Monoclonal - Omalizumab

• Used in allergic asthma for those who have failed all conventional treatment.
• Initiated only by specialists (£256 per 1ml).
• Given by subcutaneous injection every 2-4 weeks – dose varies for bodyweight and IgE concentration

• Little evidence so manufacturer advises caution in hepatic and renal disease.

• Side effects are legion. Can cause hypersensitivity reactions.
Other Asthma Medications

**Note**, you can get compound medications which are mixtures of two drugs, e.g.:
- $\beta_2$-agonist and steroid e.g. Symbicort
- $\beta_2$-agonist and anti-muscarinic e.g. Combivent

**Magnesium Sulphate**
- 1.2-2g given by IV infusion over 20 minutes
- Used in acute severe asthma.
- Believed to antagonise calcium; raised intracellular calcium causes histamine release and bronchospasm.
- Caution in kidney disease due to renal excretion. Side effects: As per hypermagnesaemia – nausea, vomiting, thirst, hypotension, arrhythmias, weakness, respiratory depression, coma.

**Cromoglicate**
- Inhaled 10mg qds up to 6-8 times daily.
- Mode of action is not completely understood although believed to stabilise mast cells, reducing cytokine release.
- Side effects are usually local – throat irritation, cough. Paradoxical bronchospasm can occur.
Pregnancy and Breastfeeding with Asthma

- It is important to maintain adequate control of asthma during pregnancy.
- ~1/3 will get better, ~1/3 will get worse, ~1/3 will stay the same
- All medications are considered safe for breastfeeding

- β-agonists – deemed safe in all forms
- Inhaled steroids – safe
- PO steroids – may increase congenital defects if used in first trimester, but shouldn’t be withheld if asthma is severe
- Xanthines - reports of neonatal apnoeas and irritable infants, but still indicated as safe.
- Leukotriene inhibitors - continue if demonstrable benefit
- No human studies for Omalizumab yet.
Other COPD Medications

**Carbocisteine**
- Given orally – 375mg tablets
- Mucolytic which reduces mucus viscosity. Shown to reduce exacerbations in those with productive coughs.
- Caution in those with previous gastric ulcer disease due to effects on gastric mucosal barrier.

**Roflumilast**
- Given orally – 500μg od.
- Is a Phosphodiesterase Type-4 Inhibitors
- Licensed as an adjunct to bronchodilators in severe COPD associated with bronchitis.
- Caution in hepatic disease, latent infection and past psychiatric disease. Side-effects: gastrointestinal disturbance, myalgia and mood change.

**Doxapram**
- 1.5-4mg/min
- Is a respiratory stimulant and only recommended when non-invasive ventilation is considered inappropriate
- Stimulates chemoreceptors in the carotid bodies of the carotid arteries, which in turn, stimulates the respiratory centre in the brain stem.
- Side-effects/Cautions – see BNF!
(Briefly:) Long Term Oxygen Therapy

Main eligibility criteria in adults:

- Patients with PaO2 of <7.3 when stable (no infection) in air.
- Patients with a PaO2 of 7.3-8kPa with evidence of polycythaemia, nocturnal hypoxaemia, peripheral oedema or pulmonary hypertension.

- Also used in chronic severe asthma, cystic fibrosis, neuromuscular conditions, chronic lung disease of prematurity etc.

- Benefit is only seen with use of more than 15 hours a day.
- Substantial benefit only seen with over 19 hours use a day.

- Patients require lots of education and regular review.
- Smoking can cause burns and explosions!

Acute Oxygen delivery, including NIV, is covered in a separate talk.
Summary

• Many of the same drugs are used in both asthma and COPD, albeit with differing importance.
• Inhaled treatments are preferred where possible, so as to limit systemic absorption.
• Nebulised treatments are the mainstay in the acute setting.
• As with most conditions, MDT input, education and lifestyle advice is important.

• The following slides provide brief summaries of the management of acute and chronic asthma/COPD.
Long Term Management of Asthma in Adults

<table>
<thead>
<tr>
<th>Asthma - suspected</th>
<th>Asthma - diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis and assessment</td>
<td>Evaluation: • assess symptoms, measure lung function, check inhaler technique and adherence • adjust dose • update self-management plan • move up and down as appropriate</td>
</tr>
</tbody>
</table>

- **Regular preventer**
  - Low-dose ICS
    - Add inhaled LABA to low-dose ICS (normally as a combination inhaler)
      - If benefit from LABA but control still inadequate - continue LABA and increase ICS to medium dose
      - If benefit from LABA but control still inadequate - continue LABA and ICS and consider trial of other therapy - LTRA, SR theophylline, beta agonist tablet, LAMA

- **High-dose therapies**
  - No response to LABA - stop LABA and consider increased dose of ICS
  - Consider trials of:
    - Increasing ICS up to high dose
    - Addition of a fourth drug, eg LTRA, SR theophylline, beta agonist tablet, LAMA
  - Use daily steroid tablet in the lowest dose providing adequate control
  - Maintain high-dose ICS
  - Consider other treatments to minimize use of steroid tablets

- **Continuous or frequent use of oral steroids**
  - Refer patient for specialist care

- **Infrequent, short-lived wheeze**
  - Consider monitored initiation of treatment with low-dose ICS

- **Short acting β₂ agonists as required** - consider moving up if using three doses a week or more

Move up to improve control as needed
Move down to find and maintain lowest controlling therapy
*Acute Asthma Exacerbation Management

- O2 via Non-Rebreathe mask
- Nebulised Salbutamol (2.5-5mg)
- Nebulised Ipratopium (500µg)
- Corticosteroids (100-200mg IV, 40mg PO)
- IV MgSO$_4$ (1.2-2g) (*Consider in acute severe asthma*)
  - IV Salbutamol (5µg/min)
  - IV Aminophylline (5mg/kg loading then 500mcg/kg/hr)

*Brief overview of...* (Check following website for more detail: http://tinyurl.com/asthmaquickreference)
Long Term Management of COPD

I: Mild
- FEV₁/FVC < 0.70
- FEV₁ ≥ 80% predicted

Add active reduction of risk factor(s); influenza vaccination
Add short-acting bronchodilator (when needed)

II: Moderate
- FEV₁/FVC < 0.70
- 50% ≤ FEV₁ < 80% predicted

Add regular treatment with one or more long-acting bronchodilators (when needed); Add rehabilitation

Add inhaled glucocorticosteroids if repeated exacerbations
Consider theophylline

III: Severe
- FEV₁/FVC < 0.70
- 30% ≤ FEV₁ < 50% predicted
- Moderate hypoxaemia, or moderate hypercapnia

Add inhaled glucocorticosteroids
Add long term oxygen if chronic respiratory failure
Consider surgical treatments

IV: Very Severe
- FEV₁/FVC < 0.70
- FEV₁ < 30% predicted or FEV₁ < 50% predicted plus chronic respiratory failure

*Brief overview of... (See www.nice.org.uk/nicemedia/live/13029/49399/49399.pdf or OHCM)
**Acute COPD Exacerbation Management**

- **Controlled Oxygen Therapy**  
  *(remember, hypoxia kills before hypercapnia)*

- **Nebulised Salbutamol and Ipratropium**

- **IV or PO corticosteroids**

- **Are Antibiotics Needed?**

- **Consider Non-invasive ventilation**  
  - Consider Theophylline

---

*Brief overview of...*  
(See www.nice.org.uk/nicemedia/live/13029/49399/49399.pdf or OHCM)
Thank-You

Any Questions?