Faculty of Medicine
Department of pharmacology
respiratory module
2014-2015
Pharmacotherapy of bronchial asthma
At the end of this lecture, the students should be able to:
1. Describe the strategies of drug treatment of bronchial asthma.
2. List the major classes of drugs used in asthma.
3. Describe the mechanisms of action of these drug groups.
4. Describe the pharmacodynamics of these drugs.
5. Describe the pharmacokinetics of these drugs.
6. Describe the pharmacological actions of these drugs.
7. List the major adverse reactions of the most important drug groups.
8. List drug-drug interactions.
Outline of lecture

• Definition of asthma and its types.

• Causes.

• Pathology of asthma

• Treatment of asthma according to its type and severity.
Bronchial asthma

• Asthma: is defined as a recurrent *reversible* airway obstruction.

• *Airway hyper responsive!!!* due to variety of stimuli

**Symptoms**

• It is comprised cough, wheezing and difficulty in breathing.

• Sever attacks may cause hypoxemia and are life–threatening.
Common asthma Triggers

- Allergic trigger
  - molds
  - animals
  - feathers
  - certain foods
  - pollen
- Non-allergic trigger
  - Cold or humid air
  - Exercise
  - Stress
  - Infection (flu or cold)
  - Cigarette smoke
  - Dust
Pathophysiology of asthma

Normal bronchial epithelium
- Mucous gland
- Mucous cell
- Blood vessel
- Bronchial smooth muscle
- Vagus nerve (efferent)

Hyperresponsive condition
- Infiltrating eosinophils
- Epithelial shedding
- Hypersecreting Mucous gland
- Leaking blood vessel
- Constricted smooth muscle
- Vagus nerve (efferent)

Trigger Factor
- Airway Inflammation
- Mucus Production
- Airway Muscle Tightening
- Swollen Bronchial Membranes
- Narrow Breathing Passages
- Wheezing, Cough, Shortness of Breath
A Normal

Muscle of bronchi are relaxed, allowing easy airflow.

Normal bronchial tube

B Asthma

Muscles of bronchi are tight and thickened. The bronchi are inflamed and filled with mucus, which impedes airflow.

Inflamed bronchial tube
Classification of Asthma

Intermittent.
- Difficulty breathing, wheezing, chest tightness and coughing
- Fewer than 2 days a week

Mild persistent.
- Symptoms occur on more than 2 days a week

Moderate persistent.
- Symptoms occur daily
- Needs treatments (short acting inhaler)

Severe persistent.
- The symptoms occur throughout each day (Continual).
Treating asthma

- No cure for asthma.
- Managed by using medication and trigger avoidance.
Think

From the pathophysiology of asthma
Can you figure out what do we need to treat patient with asthma?
### Treatment of asthma

#### Muscles relaxant drugs
1. B2 agonist
2. Methylxanthines
3. Muscarinic
4. **Leukotriene inhibitorsantagonist**

#### Anti-inflammatory drugs
1. Corticosteroids
2. Cromolyn & Nedocromil
3. Omalizumab
4. **Leukotriene inhibitorsantagonist**
Asthma treatment

- Reliever
- Controller
- Prophylaxis
1. B2 Adrenergic agonist

Short acting SABA
- Rapid onset (5-30 min)
- Provide relief for 4-6 hrs.
- Solely therapy for mild intermittent asthma.
- Relief acute bronchial asthma
- Give via oral and inhalation.

Ex: terbutaline, albuterol and Salbutamol

Long acting LABA
- Slower onset of action!!!
- Long acting for 12 hrs
- Should be given with inhaled corticosteroid (ICS).
- Give via inhalation only.

Ex: Salmeterol and formoterol
**Bronchodilation**

- **Beta 2 agonists**
  - Asthmatic bronchiole
  - Mucus gland
  - Smooth muscle
  - Bronchodilation

**Diagram:**
- **Agonist**
- **Beta receptor**
- **G_{s}**
  - GDP
  - GTP
- **Adenylyl cyclase**
- **ATP**
- **cAMP**
- **Bronchodilation**
Adverse effects

Tachycardia
 hyperglycemia
 Hypokalemic
 Tremor
 Tolerance
2. Muscarinic drug antagonist

- Inhaled bronchodilator → anticholinergic drugs e.g. *atropine*
  - ipratropium and tiotropium

- Drug of choice in obstructive pulmonary disease COPD patients.

- Can be companied with B2 agonist to provide great bronchodilator
  e.g. albuterol and ipratropium or salmeterol and tiotropium.

- Ipratropium Nearly free of side effects.
3-Methylxanthines

- e.g. theophylline, aminophylline and proxifylline.

- Use for acute asthma.

- Largely replaced by B2 agonist and corticosteroid.

- Metabolize in liver (drug – drug interaction)
Theophylline Mechanism of action

Bronchodilation

Bronchial tone

Bronchoconstriction

Ach → + Adenosine → +
M antagonist → -

Theophylline → -

Phosphodiesterase

cAMP

AC

B2 agonist

Theophylline
Theophylline adverse effects

- Has high side effect profile due to its narrow therapeutic index.
- Needs to be monitored in the plasma to avoid toxicity.
- It may cause seizures or potentially fatal arrhythmias at overdoses.
4. Leukotriene antagonist (prophylaxis)

- **Zileuton** a selective and specific inhibitor of 5-lipoxygenase, thereby preventing leukotriene synthesis.

- Effective in exercise and antigen-induced bronchospasm.

- Drug of use in aspirin induce asthma.

- **Zileuton** least prescribed because the requirement of 4 time dosing daily!
Leukotriene antagonist (prophylaxis)

- **Zafirlukast** and **Montelukast** selective reversible inhibit or of the cysteinyl leukotrienes from binding to its receptor, thereby preventing its action.

- **Montelukast** Appear to be safe to use, available in chewable or granule formulation and can be given for children less than 1 year and older.

- **Montelukast** prevent of exercise induce asthma.
Adverse effects

• Elevation in serum hepatic enzymes may occur.

• **Zileuton and Zafirlukast** ↓ CP450.

• Headache and dyspepsia.

• Rare report of eosinophilic vasculitis.

• Rare report of **Churg Strauss Syndrome**.
Anti-inflammatory drugs
1. Corticosteroids

• Drug of choice in any degree of persistent asthma.

• Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.

• Mediated by inhibition of production of inflammatory cytokines.
Mechanism of action

Route of administration!

**Inhalation**
- Metered-doses inhaler!
- Dry powder inhaler

**Oral/systemic**
- Sever asthma
- IV administration e.g. Methylprednisolone
- or oral prednisone

**Spacers**
Large-volume chamber attached to metered-doses inhaler.
Adverse effects

- Oropharyngeal candidiasis and hoarseness voice
- To minimize these problems...

**Figure 27.4**
Pharmacokinetics of inhaled glucocorticoids. GI = gastrointestinal.
2. Cromolyn and nedocromil

- Prophylactic anti-inflammatory agents.
- **NOT** for acute asthma.
- **Mechanism of action:**
  - Inhibits inflammatory cell activation.
  - Inhibits mast cell degranulation.
  - Inhibits release of histamine.
Cromolyn and nedocromil

• Because its poorly absorbed
  ➢ Cromolyn is available as a nebulized solution.
  ➢ Nedocromil aerosol form only
  ➢ Minor side effects are linked to it.

• Pretreatment with cromolyn blocks allergen- and exercise-induced bronchoconstriction.

• Cromolyn solution is also useful in reducing symptoms of allergic rhinoconjunctivitis and Allergic rhinitis.
Cromolyn and nedocromil

- Cromolyn is safe and recommended in children and pregnant.
- Due to short duration of action it require frequent dosing.

So what!!
Omalizumab

- Useful for treatment for moderate to severe allergic asthma in patients who are poorly controlled with other conventional therapy.

- It is not presently used as first line therapy due to
  - the high cost of the drug.
  - limitations on dosage.
  - limited clinical trial data.
## Treatment of Asthma

<table>
<thead>
<tr>
<th>Step</th>
<th>Condition</th>
<th>Long-term preventive</th>
<th>Quick relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><strong>Severe Persistent Asthma</strong></td>
<td>High dose inhaled steroids + LABA + oral steroids</td>
<td>Salbutamol SOS</td>
</tr>
<tr>
<td>3</td>
<td><strong>Moderate Persistent Asthma</strong></td>
<td>Medium dose inhaled steroids + LABA / leukotriene modifiers</td>
<td>Salbutamol SOS</td>
</tr>
<tr>
<td>2</td>
<td><strong>Mild Persistent Asthma</strong></td>
<td>Low dose inhaled steroids/cromoglycate/leukotriene modifiers</td>
<td>Salbutamol SOS</td>
</tr>
<tr>
<td>1</td>
<td>Intermittent</td>
<td>None</td>
<td>Salbutamol SOS</td>
</tr>
</tbody>
</table>
Thank you