Drugs Acting on Respiratory System

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EXPECTATIONS...?????
It's Quiz Time!
1. What do we mean by Asthma..?
2. What are the symptoms of asthma..?
3. Mention two drugs used for treatment of asthma..?
4. What do we mean by mast cell stabilizers..?
5. What is the mechanism of action of Montelukast..?
OBJECTIVES:

By the end of this lecture student should have knowledge about:

1. Asthma and its clinical presentation.
2. Different classes of drugs used for asthma treatment.
3. Important ADRs of these drugs.
I. Drug Therapy of Bronchial Asthma
• The term *asthma* is derived from the Greek word meaning *difficulty in breathing*.

• Asthma is a chronic inflammatory allergic disease: the patients suffer with *reversible* episodes of airways obstruction due to bronchial hyper-responsiveness.
• In the **Early (acute) phase** there are smooth muscle spasm and excessive bronchial secretion of mucus.

• In the late **Chronic (delayed) phase**, inflammation continues, accompanied by fibrosis, oedema and necrosis of bronchial epithelial cells.
Asthma is characterized

Clinically by recurrent bouts of coughing, shortness of breath, chest tightness, and wheezing.

Physiologically by widespread, reversible narrowing of the bronchial airways and a marked increase in bronchial responsiveness to inhaled stimuli.

Pathologically by lymphocytic, eosinophilic inflammation of the bronchial mucosa.
• **The cardinal symptoms of asthma** are breathlessness, wheezing, cough and chest tightness with worsening of these symptoms at night. In the acute attack there are rapid respiratory rate and tachycardia.
• The majority of patients suffer with **atopic extrinsic asthma**, which is associated with exposure to specific allergen (pollen or house-dust mite).
• In **non-atopic extrinsic asthma** the attack may be stimulated with some non-specific stimulus, e.g. chemical irritants.
• **Classification of Antiasthmatic Drugs**

1. Bronchodilators
   - **Selective $\beta_2$-agonists**: Salbutamol, Terbutaline, Fenoterol, Indacaterol, Levosalbutamol, Salmeterol,
   - **Nonselective $\beta$-agonists**: Epinephrine, Isoprenaline, Orciprenaline; Ephedrine
   - **$M$-cholinolytics**: Ipratropium, Tiotropium, Oxitropium
   - **Methyl Xanthines**: Theophylline, Aminophylline, Theotard
2. Glucocorticosteroids (GCS)

- **Oral:** Prednisone, Methylprednisolone
- **Parenteral:** Methylprednisolone, Betamethasone
- **Inhalational:** Beclomethasone, Budenoside, Fluticasone, Triamcinolone

3. Inhalational $\beta_2$-agonists/Glucocorticosteroids

- Seretide® (fluticasone/salmeterol)
- Symbicort® (budenoside/formoterol)
4. Leukotriene Modulators

- 5-Lipoxygenase Inhibitor: Zileuton

- LTD$_4$-antagonists: Zafirlukast, Montelukast

5. Monoclonal Anti-IgE Antibody: Omalizumab
1. Bronchodilators – Relievers
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- provide a rapid symptomatic relief but they *Do Not* control the disease process.
1. Epinephrine:

- Is an effective, rapidly acting bronchodilator when injected subcutaneously (0.4 mL of 1:1000 solution) or inhaled as a microaerosol from a pressurized canister (320 mcg per puff).
- Maximal bronchodilation is achieved 15 minutes after inhalation and lasts 60–90 minutes.
Because epinephrine stimulates $\alpha$ and $\beta_1$ as well as $\beta_2$ receptors, tachycardia, arrhythmias, and worsening of angina pectoris are troublesome adverse effects.
2. Selective \( \beta_2 \)-agonists:

activate \( \beta_2 \)-receptors present on airway smooth muscle and mast cells too.

- These agents relax airway smooth muscle, inhibit the release of bronchoconstricting mediators from the adipocytes and increase the mucociliary transport by increasing the mucociliary activity.
**ADRs:**

Tremor, Tachycardia, Desensitization/down-regulation of $\beta_2$-receptors that results in diminished responsiveness.
The $\beta_2$-adrenoceptor agonists are usually given by inhalation of aerosol, powder or nebulized solution (i.e. solution that has been converted into a cloud or mist of fine droplets), but some may be given orally or by injection.
Two categories of $\beta_2$-adrenoceptor agonists are used in asthma.

**Short-acting agents:** Salbutamol and Terbutaline.

These are given by inhalation; the maximum effect occurs within 30 min and the duration of action is 3-5 h; they are usually used on an 'as needed' basis to control symptoms.
Longer-acting agents: e.g. Salmeterol and Formoterol.

These are given by inhalation, and the duration of action is 8-12 h. They are not used 'as needed' but are given regularly, twice daily, as adjunctive therapy in patients whose asthma is inadequately controlled by glucocorticoids.
3. Methylxanthines:

- (Theophylline, Aminophylline, Theotard)

- a) inhibit phosphodiesterase III (present in airway muscle) and IV (present in eosinophil and mast cells), the two specific isoenzymes responsible for the degradation of cAMP.
b) Block the adenosine-1-receptors on airway muscle and adenosine-3-receptors, present on mast cells.

The main use of methyl xanthins is in the management of asthma and COPD (Chronic Obstructive Pulmonary Disease), usually as combination therapy with beta-2-agonists.
**ADRs:**

- The therapeutic plasma concentration range is 30-100 μmol/l, and adverse effects are common with concentrations greater than 110 μmol/l.

- Serious cardiovascular and CNS effects can occur when the plasma concentration exceeds 200 μmol/l.
The most serious cardiovascular effect is **Dysrhythmia**

(especially during intravenous administration of aminophylline), which can be fatal.

**Seizures** can be fatal in patients with impaired respiration due to severe asthma.
Clinical uses of Theophylline:

- In addition to steroids, in patients whose asthma does not respond adequately to $\beta_2$-adrenoceptor agonists.

- In addition to steroids in COPD.

- Intravenously (as aminophylline, a combination of theophylline with ethylenediamine to increase its solubility in water) in acute severe asthma.
Theophylline is given orally as a sustained-release preparation.

Aminophylline can be given by slow intravenous injection of a loading dose followed by intravenous infusion.
Theophylline is well absorbed from the gastrointestinal tract. It is metabolized by CP450 enzymes in the liver; the mean elimination half-life is approximately 8 h in adults but there is wide inter-individual variation.

The half-life is increased in liver disease, cardiac failure and viral infections, and is decreased in heavy cigarette smokers???
4. Muscarinic receptor antagonists

- The main compound used as a bronchodilator is **Ipratropium**.
- **Tiotropium** is also available; it is a longer-acting drug used in maintenance treatment of COPD.
**Mechanism of Action:**

- Muscarinic antagonists competitively inhibit the effect of acetylcholine at muscarinic receptors.

- In the airways, acetylcholine is released from efferent endings of the vagus nerves, and muscarinic antagonists block the contraction of airway smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity.
**Clinical uses:**

- Ipratropium, as an adjunct to β<sub>2</sub>-adrenoceptor antagonists and steroids, for asthma.

- For some patients with COPD, especially long-acting drugs (e.g. **Tiotropium**).
Antimuscarinic drugs appear to be slightly less effective than $\beta_2$-agonist agents in reversing asthmatic bronchospasm, the addition of Ipratropium enhances the bronchodilation produced by nebulized Albuterol in acute severe asthma.

Ipratropium appears to be at least as effective in patients with COPD that includes a partially reversible component.
2. Glucocorticosteroids
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- provide long-term stabilization of the symptoms due to their anti-inflammatory effects. Inhaled GCS, along with beta-2-agonists are the first choice drugs for chronic asthma.

- GCS inhibit the release of PGs and LTs and thus prevent smooth muscle contraction, vascular permeability and airway mucus secretion.
• GCS produce eosinopenia which prevents cytotoxic effects of the mediators released from eosinophils.

• GCS enhance beta-2-adrenergic response by up-regulating the beta-2-receptors in lung cells and leuckocytes. Several hours are required for DNA transcription and RNA translation to occur after administering GCS.
**Actions and mechanism**

- They decrease formation of cytokines, in particular the cytokines that recruit and activate eosinophils and are responsible for promoting the production of IgE and the expression of IgE receptors. Glucocorticoids also inhibit the generation of the vasodilators PGE$_2$ and PGI$_2$, by inhibiting induction of COX-2.
The *anti-inflammatory actions* of GCS are mediated by stimulation of synthesis of lipocortin, which inhibits pathways for production of PGs, LTs and others. These mediators would normally contribute to increased vascular permeability and subsequent changes including oedema, leukocyte migration, fibrin deposition.
The main compounds used are **Beclometasone**, **Budesonide**, **Fluticasone**, **Mometasone** and **Ciclesonide**. These are given by inhalation with a metered-dose or dry powder inhaler, the full effect on bronchial hyper-responsiveness being attained only after weeks or months of therapy.
The most used glucocorticoids

Hydrocortisone

Prednisolone

Nonfluorinated prednisolones
- Methylprednisolone

Fluorinated prednisolones
- Betamethasone, Dexamethasone
- Fluticasone, Triamcinolone
Clinical use of glucocorticoids in asthma:

- Patients who require regular bronchodilators should be considered for glucocorticoids treatment (Beclometasone).
- More severely affected patients are treated with high-potency inhaled drugs (Budesonide).
Patients with acute exacerbations of asthma may require intravenous **Hydrocortisone** and oral **Prednisolone**.

A 'rescue course' of oral **Prednisolone** may be needed at any stage of severity if the clinical condition is deteriorating rapidly.
Prolonged treatment with oral \textit{Prednisolone}, in addition to inhaled bronchodilators and steroids, is needed by a few severely asthmatic patients
**ADRs:**

- Serious unwanted effects are uncommon with inhaled steroids.
- Oropharyngeal candidiasis can occur, as can sore throat and croaky voice, but use of 'spacing' devices, which decrease oropharyngeal deposition of the drug and increase airway deposition, reduces these problems.
- Regular high doses can produce some adrenal suppression, particularly in children.
Adverse effects of GCS

- Cushing’s syndrome
- Osteoporosis
- Tendency to hyperglycemia
- Negative nitrogen balance
- Increased appetite
- Increased susceptibility to infections
- Obesity etc.
3. Leukotriene Modulators
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- Metabolism of arachidonic acid via 5-lipoxigenase pathway yields the cysteinyll LTs – C4, D4 and E4, which activate cysteinyll leukotriene receptors to cause bronchoconstriction, stimulate mucus secretion and increase capillary permeability, leading to pulmonary oedema.
The asthma attack is thought to result from inhibition of prostaglandin synthetase (Cyclooxygenase), shifting Arachidonic acid metabolism from the prostaglandin to the leukotriene pathway.
Arachidonic acid

5-Lipoxigenase

Leukotrienes (LTs)

LTC - receptor

LTD - receptor

LTE - receptor

Montelukast, Zafirlukast
• Two approaches to interrupting the leukotrienes pathway:

1. Inhibition of 5-lipoxygenase, thereby preventing Leukotriene synthesis e.g. Zileuton

2. Inhibition of the binding of LTD$_4$ to its receptor on target tissues, thereby preventing its action e.g. Zafirlukast and Montelukast
• They are taken orally; some patients-especially children—comply poorly with inhaled therapies.

• Montelukast is approved for children as young as 6 years of age.

• Zileuton is approved for use in an oral dosage of 400–800 mg for administration 2–4 times daily; Zafirlukast, 20 mg twice daily; and Montelukast, 10 mg (for adults) or 4 mg (for children) once daily.
4. Mast cell stabilizers
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- Prevent transmembrane influx of calcium ions, provoked by antigen-IgE antibody reaction on the mast cell membrane. They prevent degranulation and release of histamine and other autacoids from mast cells.

- They also inhibit leukocyte activation and chemotaxis.

- Indications: prophylactic treatment of asthma.
Cromoglycate – per inh.

Ketotifen (p.o.)

Nedocromil – per inh.
5. Monoclonal Anti-IgE Antibody
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- **Omalizumab**

- is a recombinant humanized monoclonal antibody.
  - It inhibits the binding of IgE to mast cells and basophils;
  - it inhibits the activation of IgE already bound to mast cells and prevents their degranulation;
  - it down-regulates Fc epsilon receptor-1, present on mast cells and basophils.
Omalizumab is indicated for asthmatic patients who are not adequately controlled by inhaled GCS and who demonstrate sensitivity to aero-allergens.
Treatment of Status Asthmaticus

- It is a potentially life-threatening acute attack of severe asthma needing immediate treatment. Most often hospitalization is necessary.

1. A high concentration (40–60%) of O₂ is administered.
3. High doses of systemic GCS (p.o./i.v.)
4. Ipratropium through inhalation.
THAT'S THE END

IF YOU HAVE ANY QUESTIONS PLEASE FEEL FREE TO ASK??
THANKS..