



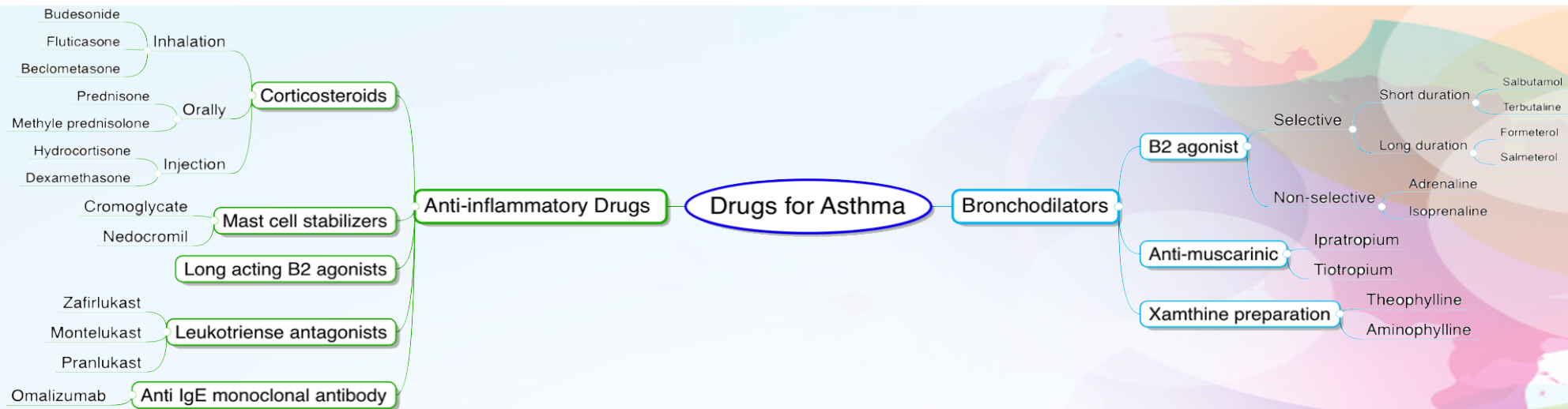
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# Drugs Used in Bronchial Asthma

# 3



RESPIRATORY BLOCK



## Main disorders of the Respiratory System

1. Bronchial asthma
2. Restrictive pulmonary disease
3. Allergic rhinitis
4. Chronic obstructive pulmonary disease (COPD, also called emphysema)

### Asthma

Asthma is a chronic inflammatory disorder of bronchial airways that result in airway obstruction in response to external stimuli (as pollen grains, cold air and tobacco smoke).

# ASTHMA

## Causes of Asthma

Infection, emotional conditions, stress, exercise, pets, seasonal changes, some drugs such as Aspirin and  $\beta$  blockers

## Characters of airways in asthmatic patients

Airway hyper-reactivity

Abnormal sensitivity of airways to wide range of external stimuli.

Inflammation

Swelling - Thick mucus production.

Broncho-spasm

constriction of the bronchial muscles.

## Symptoms of asthma

### Recurrent episodic attack of:

- Acute broncho-constriction
- Shortness of breath
- Chest tightness
- Wheezing
- Rapid respiration
- Cough

**\*Symptoms can happen each time the airways are irritated by inhaled irritants or allergens**

## Airways Innervations

### Afferent nerves (sensory):-

- Irritant receptors in upper airways.
- C-fiber receptors in lower airways.

#### Stimulated by :

- Exogenous chemicals.
- Physical stimuli (cold air).
- Endogenous inflammatory mediators e.g.Histamine.

### Efferent nerves (motor):-

#### -Parasympathetic supply:

M3 receptors in smooth muscles and glands (bronchoconstriction – increase mucus secretion).

#### -No sympathetic supply:

but  $\beta_2$  receptors in smooth muscles and glands (bronchodilation – decrease mucus secretion).

## Anti Asthmatic Drugs:

### 1) Quick relief medications:

Bronchodilators used to relieve acute episodic attacks of asthma.

### 2) Control therapy (prophylactic drugs):

anti-inflammatory drugs used to reduce the frequency of attacks, and nocturnal awakenings.

# Anti Asthmatic Drugs

## Bronchodilators (Quick relief medications)

treat acute episodic attack of asthma(bronchoconstriction):-

- Short acting " **$\beta$ 2-agonists**"
- Antimuscarinics
- Xanthine preparations

## Anti-inflammatory Agents (control medications or prophylactic therapy)

reduce the frequency of attacks:-

- Corticosteroids.
- Mast cell stabilizer.
- Leukotrienes antagonists.
- Anti-IgE monoclonal antibody.
- Long acting  $\beta$ 2-agonists.

## Sympathomimetics $\beta$ 2- adrenoceptor agonists

Mechanism of Action:

- direct  $\beta$ 2 stimulation  $\rightarrow$  stimulate adenylyl cyclase  $\rightarrow$  Increase cAMP  $\rightarrow$  bronchodilation
- Inhibit mediators release from mast cells.
- Increase mucus clearance by (increasing ciliary activity).

# Classification of $\beta_2$ agonists:

## 1- Non selective $\beta$ agonists: Epinephrine, Isoprenaline.

Epinephrine	
characterized by	Bronchodilator, rapid action(5 min), given subQ or by inhalation, short duration of action (60-90min).
contraindication	CVS patients, diabetic patients.
Disadvantages	Not effective orally, Hyperglycemia, tachycardia, arrhythmia, hypertension, tremor, not used for asthmatic patients with CVD.
Drug of choice for	acute anaphylaxis, hypotension, bronchoconstriction.

## 2- Selective $\beta_2$ –agonists: ( Preferable)

**Short acting** :Salbutamol, Terbutaline.

**Long acting** : Salmeterol, Formeterol .

	Short acting	Long acting (12hr)
characterized	Rapid onset of action(15-30min). short duration (4-6hr). <b>Salbutamol</b> given orally, inhalation, and <b>I.V. Terbutaline</b> given orally, inhalation, and <b>S.C.</b>	high lipid solubility, given by inhalation, combined with inhaled corticosteroids to control asthma, minimal CVS side effects , used for asthmatic patients with <b>CVD</b> and hypertension .
Disadvantages	-	Tremors, Nervousness, Tolerance, Tachycardia (over dose) .
Drug of choice for	symptoms of acute episodic attack of asthma	nocturnal asthma الربو الليلي

## Muscarinic antagonists

### Ipratropium

short duration of action 3-5 hr

### Tiotropium

longer duration of action (24 h).

\*Act by blocking muscarinic receptors.

\*Given by aerosol inhalation.

\*Quaternary derivatives of atropine.

\*Does not diffuse into the blood.

\*Do not enter CNS, minimal systemic side effects.

\*Delayed onset of action.

### Pharmacodynamics

- Are short-acting bronchodilator.
- Inhibit bronchoconstriction and mucus secretion.
- Less effective than  $\beta$ 2-agonists.
- No anti-inflammatory action.

### Uses

- Main choice in chronic obstructive pulmonary diseases (COPD).
- In acute severe asthma combined with  $\beta$ 2-agonists & steroids (corticosteroids).

## Methylxanthines: Theophylline & Aminophylline

<b>mechanism of action</b>	<ul style="list-style-type: none"> <li>-phosphodiesterase inhibitor → increases cAMP → bronchodilation.</li> <li>-Universal Adenosine receptors (A1) antagonists → prevent bronchoconstriction.</li> <li>-Increase diaphragmatic contraction.</li> <li>-Stabilization of mast cell membrane.</li> </ul>
<b>Pharmacological effects :</b>	<ul style="list-style-type: none"> <li>-Bronchial muscle relaxation.</li> <li>-↑contraction of diaphragm→ improve ventilation.</li> <li><b>CVS:</b> ↑ heart rate, ↑ force of contraction.</li> <li><b>GIT:</b> ↑ gastric acid secretions.</li> <li><b>Kidney:</b> ↑renal blood flow, weak diuretic action.</li> <li><b>CNS stimulation:</b> stimulant effect on respiratory center, decrease fatigue and elevate mood, overdose causes (tremors, nervousness, insomnia, convulsion).</li> </ul>
<b>Pharmacokinetics:</b>	<ul style="list-style-type: none"> <li>-metabolized by <b>Cyt P450</b> enzymes in liver. T<sub>1/2</sub>= 8 hours</li> <li><b>-Drug interactions:-</b> <ul style="list-style-type: none"> <li>Enzyme inducers: as phenobarbitone and rifampicin → ↑metabolism of theophylline → ↓ T<sub>1/2</sub>.</li> <li>Enzyme inhibitors: as erythromycin→ ↓ metabolism of theophylline → ↑T<sub>1/2</sub>.</li> </ul> </li> </ul>
<b>Uses:</b>	<ul style="list-style-type: none"> <li>-Second line drug in asthma (<b>theophylline</b>, is given orally)</li> <li>-For status asthmatics (<b>aminophylline</b>, is given as slow infusion).</li> </ul>
<b>Side Effects:</b>	<ul style="list-style-type: none"> <li>-<b>Low therapeutic index</b> narrow safety margin ,monitoring of theophylline blood level is necessary.</li> <li><b>CVS effects:</b> hypotension, arrhythmia.</li> <li><b>GIT effects:</b> nausea &amp; vomiting.</li> <li><b>CNS side effects:</b> tremors, nervousness, insomnia, convulsion.</li> </ul>

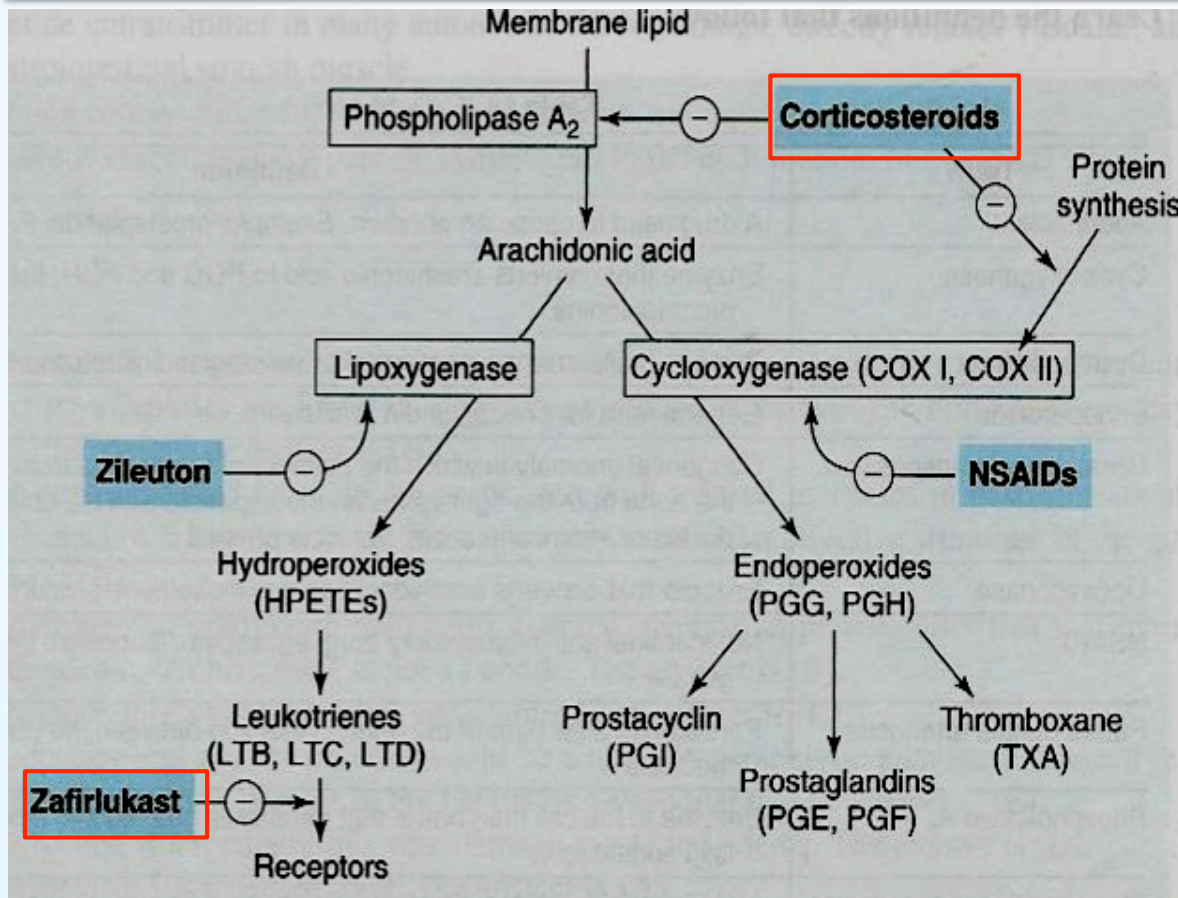


# Prophylactic Therapy

## Anti-inflammatory drugs

- 1-Glucocorticoids.
- 2-Leukotrienes antagonists.
- 3-Mast cell stabilizers.
- 4-Anti-IgE monoclonal antibody.

Actions: reduce inflammation and spasm of the airways, reduce bronchial hyper-reactivity.



### Inflammatory Pathway

-Corticocorticoids inhibit all the rest of the pathway.

# 1 - Glucocorticoids

## Mechanism of action

It has anti-inflammatory action due to:

Inhibition of phospholipase A2

- ↓ prostaglandin and leukotrienes
- ↓ Number of inflammatory cells in airways.
- Mast cell stabilization → ↓ histamine release.
- ↓ capillary permeability and mucosal edema.
- Inhibition of antigen-antibody reaction.
- Upregulate  $\beta_2$  receptors (have additive effect to  $\beta_2$  agonists).

## Pharmacological actions (wanted actions)

- Anti-inflammatory actions.
- Immunosuppressant effects "suppress antigen-antibody effects"
- Reduce bronchial inflammation.
- Reduce bronchial hyper-reactivity to stimuli.

## Metabolic effects (unwanted actions)

- \* On carbohydrates: Hyperglycemia
- \* On proteins: ↑ protein catabolism, ↓ protein anabolism
- \* On lipids: Stimulation of lipolysis, fat redistribution → moonface

## Mineralocorticoid effects (unwanted actions)

- Sodium/fluid retention → edema
- Increase potassium excretion (hypokalemia).
- Increase blood volume (hypertension).

## Pharmacokinetics

- \* Have delayed onset of action (effect usually attained after 2-4 weeks).
- \* Maximum action at 9-12 months.

# 1 - Glucocorticoids

## Administration

### Inhalation:

#### e.g. **Budesonide & Fluticasone, beclometasone**

Given by inhalation (metered-dose inhaler). "local action".  
Have first pass metabolism "minimizes side effects".  
Best choice in asthma, less side effects.

**Orally:** Prednisone, methyl prednisolone.

**Injection:** Hydrocortisone, dexamethasone

## When to use

- Given as prophylactic medications, used alone or combined with  $\beta_2$  agonists.
- Effective in allergic, exercise, antigen and irritant-induced asthma,
- Systemic corticosteroids are reserved for: Status asthmaticus (i.v.).

### **Inhaled steroids should be considered for adults, children with any of the following features:**

- using inhaled  $\beta_2$  agonists three times/week
- symptomatic three times/ week or more;
- or waking one night/week.

(bronchodilators will only treat at the time of the attack but won't stop the recurrent attacks like these)

## Clinical uses

1. Treatment of **inflammatory disorders** (asthma, rheumatoid arthritis).
2. Treatment of **autoimmune disorders** (ulcerative colitis, psoriasis الصدفية ) and after organ or bone marrow transplantation.
3. **Antiemetics** in cancer chemotherapy.

# 1 - Glucocorticoids

## Side effects

- Adrenal suppression
- Growth retardation in children "when given systemically"
- Susceptibility to infections "because it suppress the immune system"
- Fluid retention → weight gain → hypertension
- Hyperglycemia
- Fat distribution → moonface
- Cataract (an optic disorder)
- Behavioral changes: depression
- Bone loss (osteoporosis) due to
  - \*Inhibit bone formation.
  - \*↓ calcium absorption from GIT.
- Psychosis

### **Inhalation has very less side effects:**

- \*Oropharyngeal candidiasis (thrush).
- \*Dysphonia (voice hoarseness).

## Withdrawal

Abrupt stop of corticosteroids should be avoided and dose should be tapered (adrenal insufficiency syndrome).

- \*So when we're going to stop this medication, we should stop it gradually.

## 2-Leukotrienes Antagonists

### Overview

- Synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells).
- Produced by the action of 5-lipoxygenase on arachidonic acid. "look at the inflammatory pathway"
- **Leukotriene B4:** chemotaxis of neutrophils "attraction of them to the site of inflammation"
- **Cysteinyl leukotrienes C4, D4 & E4:**
  - \*bronchoconstriction
  - \*increase bronchial hyper-reactivity
  - \*↑ mucosal edema, ↑ mucus secretion

### Zafirlukast, Montelukast, Pranlukast

- Are selective, reversible antagonists of cysteinyl leukotriene receptors (CysLT<sub>1</sub> receptors). ← they block this receptor.
- Taken orally.
- **Are bronchodilators.** "but cannot be used in acute asthma attack because their main action is anti-inflammation"
- Have anti-inflammatory action.
- Less effective than inhaled corticosteroids.
- Have glucocorticoids sparing effect (potentiate corticosteroid actions). "reduce the dose of corticosteroids when they're combined with them".

### Uses

- \***Prophylaxis** of mild to moderate asthma.
  - \*Aspirin-induced asthma
  - \*Antigen and exercise-induced asthma
  - \*Can be combined with glucocorticoids

### Side effects:

Elevation of liver enzymes, headache, dyspepsia

# 3- Mast Cell Stabilizers

## Nedocromil - Cromoglycate

### Pharmacokinetics

Administration: by inhalation (aerosol, nebulizer).  
Absorption: poor absorption orally.

### Pharmacodynamics

- Are **Not** bronchodilators
- **Not** effective in acute attack of asthma.
- **Prophylactic** anti-inflammatory drug
- Reduce bronchial hyper-reactivity.
- Effective in exercise, antigen and irritant-induced asthma.
- Children respond better than adults

### Uses

- Prophylactic therapy in asthma especially in children.
- Allergic rhinitis.
- Conjunctivitis.

### Side effects

- Bitter taste
- minor upper respiratory tract irritation (burning sensation, nasal congestion)

## 4- Anti-IgE monoclonal antibody e.g. Omalizumab

It is a monoclonal antibody directed against **human IgE**.

Expensive-not first line therapy.

### **Actions**

prevents IgE binding with its receptors on mast cells & basophiles.  
↓ release of allergic mediators.

### **Uses**

treatment of allergic asthma patients whose symptoms are not controlled with inhaled steroids.

# Summary

Asthma: is chronic inflammatory disorder.

## Characterized by :

- 1-hyper-reactivity.
- 2-inflammation (swelling +mucous production).
- 3-bronchospasm.

## Symptoms:

- 1-cough
- 2-dyspnea
- 3-wheezing
- 4-chest pain

## Aim of asthmatic drugs :

- 1- To relieve acute episodic attacks of asthma.
- 2- To reduce the frequency of attacks.

## Anti-asthmatic drugs :

1-bronchodilators:

-  $\beta_2$  - adrenoreceptor agonists.

\*selective as salbutamol (short acting), salmetrol(long acting).

\*Non selective as epinephrine which is Drug of choice for **acute anaphylaxis** .

## Advantages of $\beta_2$ agonists:

- 1-Minimal CVS side effects
- 2-suitable for asthmatic patients with hypertension or heart failure.

## Disadvantages of $\beta_2$ agonists:

- 1-Skeletal muscle tremors.
- 2-Nervousness
- 3-Tachycardia over dose ( $B_1$ -stimulation).

## Muscarinic antagonists:

1-Act by blocking muscarinic receptors.

2-Quaternary

3-Do not enter CNS, minimal systemic side effects.

## Such as:

1-Ipratropium has short action.

2-Tiotropium has long action.

They are Less effective than  $\beta_2$ -agonists.

3-Methylxanthines  
(Theophylline - aminophylline)

Uses

Second line drug in asthma  
(theophylline)  
status asthmatics  
(aminophylline)

## S/E:

hypotension, arrhythmia  
nausea , vomiting  
tremors, nervousness,  
insomnia, convulsion.



# MCQs

1- Which ONE of the following is Selective

$\beta$  2 –agonists :

- A- Epinephrine
- B- Salmeterol
- C- Isoprenaline
- D- None of them

2- Which ONE of the following is the drug of choice in acute anaphylaxis:

- A- Epinephrine
- B- Glycopyrrolate
- C- Norepinephrine
- D- Mixture of Salmeterol and formeterol

3- Which ONE of the following cannot be used to relieve acute episodes of asthma :

- A- Salbutamol
- B- Terbutaline
- C- Salmeterol .
- D- A&B

4-Which ONE of the following promote bronchodilaton in bronchial asthma:

- A- Increased levels of 2,3 BPG
- B- Increased intracellular calcium levels
- C- Increased cAMP levels
- D- Decreased levels of adenylyl cyclase

5- Which ONE of the following drugs has a funtion that stabilizes the mast cell actions:

- A- Theophylline
- B- Glucocorticoids
- C- Ipratropium
- D-T A&B

6- Which ONE of the following drugs should be monitored due to its narrow safety margin

- A- Theophylline
- B- Ipratropium
- C- Salbutamol
- D- Salmeterol

-Which ONE of the following is the effect of over dose of long-acting selective B2 agonists on B1 receptors stimulation:

- A- Bradychardia
- B- Tachypnea
- C- Tachycardia
- D- Cardiac arrest

- An asthmatic patient who is on methylxanthines came to the ER complaining from upper respiratory tract infection, the doctor prescribed erythromycin for him, what is the effect of of erythromycin on methylxanthines

- A- It will make it lipid insoluble
- B- It will increase its plasma half life
- C- It will decrease its plasma half life
- D- Induce its metabolism and excretion

-An asthmatic patient used one of the anti-inflammatory drugs to reduce his bronchial hypersensitivity , but after a month of taking it he gained weight and got moon-face. Which of these drugs is most likely what he's taking?

- A- Omalizumab .
- B- Prednisone.
- C- Terbutaline.
- D- Nedocromil.

10- Which of the following drugs is a bronchodilator but is not effective in acute attack of asthma .

- A- Cromoglycate.
- B- Fluticasone.
- C- Hydrocortisone.
- D- Montelukast.

1-B 2-A 3-C 4-C 5-D  
6-A 7-C 8-B 9-B 10-D



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**We hope that we made this lecture easier for you  
Good Luck !**