Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY

Respiratory Block

Drugs for Bronchial asthma and COPD

Objectives :

- ✓ Different types of drugs used for treatment of asthma.
- ✓ Differentiate between treatment and prophylactic therapy for asthma.
- ✓ Recognize the different types of bronchodilators regarding pharmacokinetics, pharmacodynamics, uses and side effects.
- ✓ Identify the different anti-inflammatory drugs for asthma in respect to kinetics, dynamics, uses and side effects.

Color index:
Red: important
Grey: Notes or extra information

Bronchial asthma

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

Characters of airways in asthmatic patients

1. **Airway hyper-reactivity (sensitivity)**: abnormal sensitivity of the airways to any external stimuli which results into release of endogenous inflammatory mediators like **histamine, leukotrienes** . **By antigen-antibody reaction (IgE)**
2. **Inflammation** (caused by hyper-reactivity)
   - A. ↑ **edema, swelling**
   - B. ↑ **Thick mucus production**
3. **Bronchospasm** (constriction of the bronchial smooth muscles).

1 —Lead to→ 2 —Lead to→ 3

Symptoms of asthma:

Asthma produces recurrent episodic attack of :-

- Acute bronchoconstriction
- Shortness of breath
- Chest tightness
- Wheezing
- Rapid respiration
- Cough

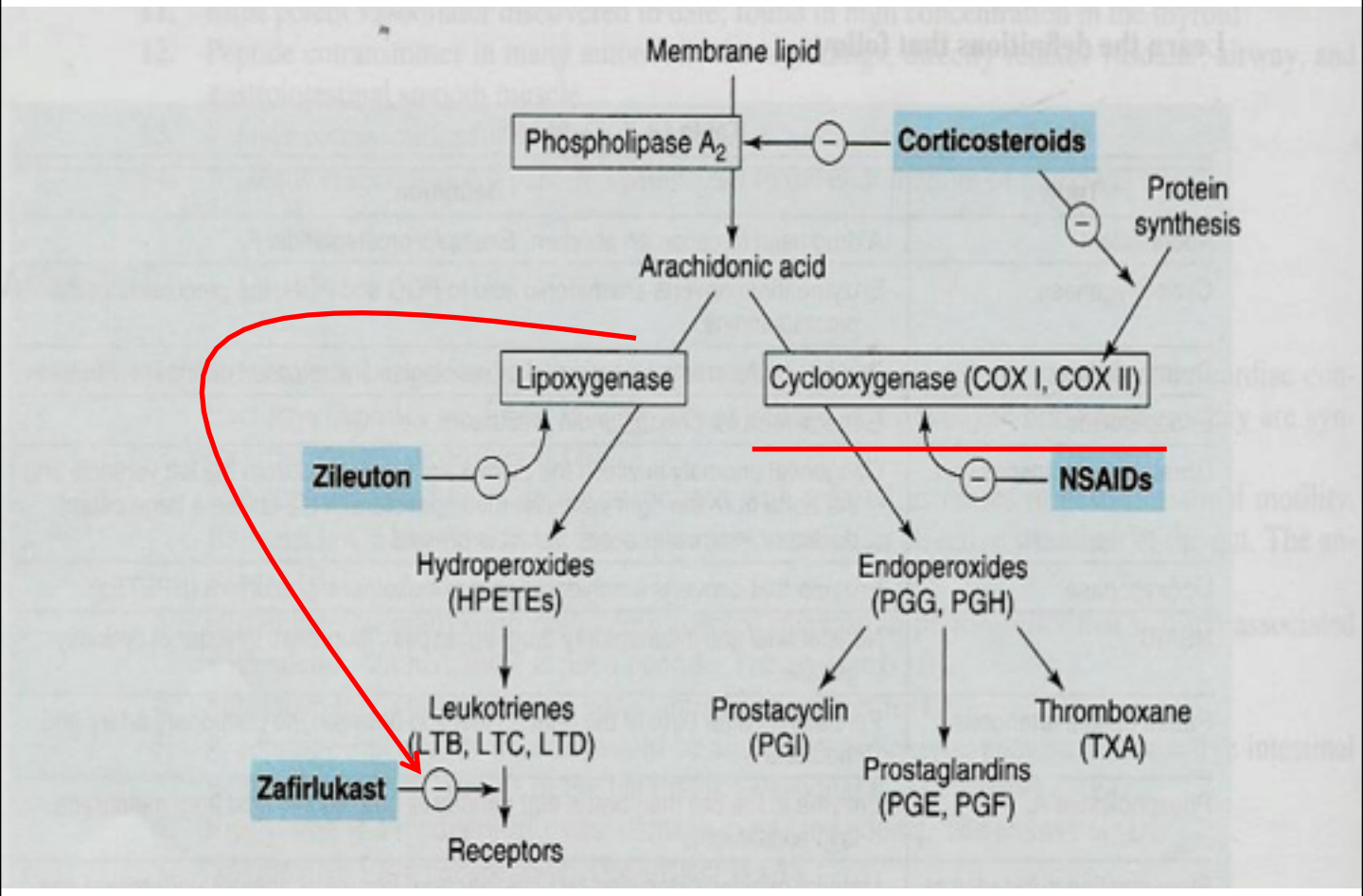
Symptoms can happen each time when the airways are irritated by inhaled irritants or allergens (triggers).

Causes of asthma

- Chest Infection
- Stress
- Exercise (cold air)
- Pets
- Seasonal changes
- Emotional conditions
- Some drugs as aspirin, β-bockers
- Exogenous chemicals or irritants (perfume)

Why aspirin will trigger asthma attacks?

Aspirin is NSAIDs drug which inhibit the cyclooxygenase , so most of arachidonic acid will convert to leukotrienes that will may lead to asthma.



Innervation of the respiratory system

- **Parasympathetic supply:-** M3 receptors in smooth muscles and glands. Causes: (Bronchoconstriction and Increase mucus secretion). That's why we block them.
- **No sympathetic supply**: but B_2 receptors in smooth muscles and glands. Causes: (Bronchodilation and Decrease mucus secretion). That's why we use it's agonist drugs.

Anti-asthmatic drugs

Treatment

Bronchodilators
(Quick relief medications)

- treat acute attack of asthma
- These drugs can produce rapid relief of bronchoconstriction

1. Short acting β2-agonists 1st choice (Sympathomimetics)
2. Anti-muscarinics 2nd choice
3. Xanthine preparations 3rd choice

Prophylactic therapy

Anti-inflammatory Agents
(As Control medications)

- reduce the frequency of attacks

1. Corticosteroids
2. Mast cell stabilizers
3. Leukotrienes antagonists
4. Anti-IgE monoclonal antibody
5. Long acting ß2-agonists

1. β- adrenoceptor agonists (Sympathomimetics)

Mechanism of Action

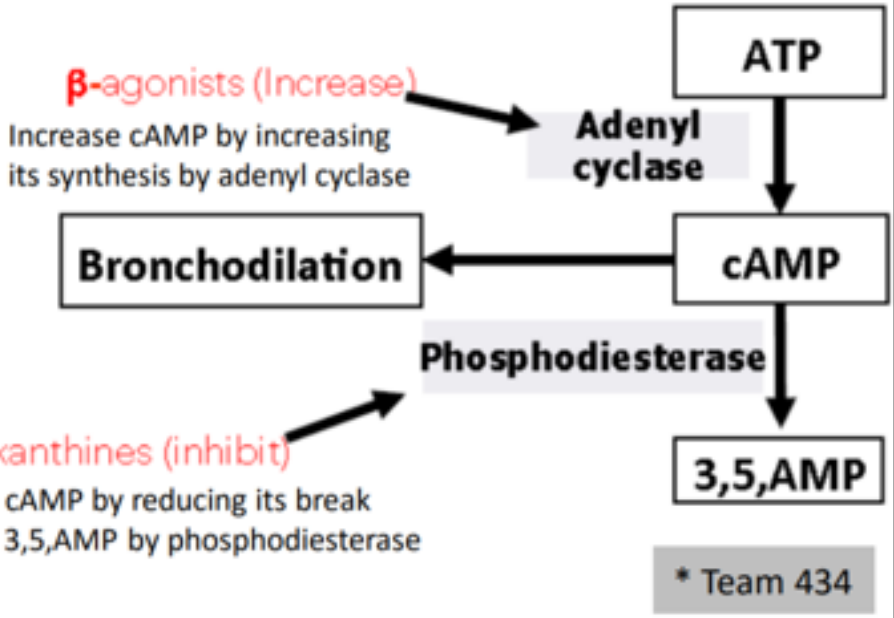
- direct β_2 stimulation →stimulate adenyl cyclase →↑ cAMP →bronchodilation.
- Increase mucus clearance by (increasing ciliary activity).
- Stabilization of mast cell membrane. (releasing of histamine will decrease).

	Non-selective β2 agonist	Selective β2 agonist (preferable)	
Examples	• Epinephrine • Norepinephrine • Isoprenaline	**Short acting:** • Salbutamol (albuterol) • Terbutaline	**Long acting:** • Salmeterol • Formoterol
Advantages	• Potent bronchodilator • Given subcutaneously (any drug that can affect the heart is given S.C not I.V to reduce the side effects on the CVS) • Rapid action (maximum effect within 15 min) • Has short duration of action (60-90 min) • Adrenaline is the drug of choice for acute anaphylaxis (hypersensitivity reaction), **can be used for asthma BUT selective B2 are better**	• Mainly given by inhalation • Can be given orally, parenterally. • Minimal CVS side effects. • Suitable for asthmatic patients with CV disorders as hypertension or heart failure.	
Disadvantages	• Not effective orally • Hyperglycaemia • Skeletal muscle tremor • CVS side effects (β 1 actions): tachycardia, arrhythmia, hypertension	• Skeletal muscle tremors • Nervousness • Tolerance (β-receptors down regulation) (due to repeated use, resulting in decrease in response) • Overdose may produce tachycardia due to β 1 stimulation	
Contraindications	• CVS patients (hypertension, heart failure) • diabetic patients		

Selective β2 -agonists

- ❖ Are mainly given by inhalation by (metered dose inhaler or nebulizer)
- ❖ Can be given orally, parenterally.

	Short acting selective ß 2 agonists	Long acting selective ß 2 agonists
Examples	• **Salbutamol** (albuterol): given by inhalation, orally , I.V (only in status asthmaticus) • **Terbutaline:** given by inhalation, orally, S.C	• Salmeterol • Formoterol Are given by inhalation.
Pharmaco-kinetics & dynamics	• Have rapid onset of action (15- 30 min) • Short duration of action (4-6 hr) • Used for acute episodic attack of asthma (drugs of choice)	• Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect). depot= storage • Are not used to relieve acute episodes of asthma • Used for nocturnal asthma • combined with inhaled corticosteroids to control asthma as prophylactic therapy (to decreases the number and severity of asthma attacks)



2. Muscarinic antagonists

	Ipratropium Short duration of action (3-5h)	Tiotropium longer duration of action (24 hrs)
Mechanism of action	• Act by blocking muscarinic receptors (non selective). • given by aerosol inhalation • Have delayed onset of action. • Quaternary derivatives of atropine (polar), So it does not diffuse into the blood & does not enter CNS. (It effect is localized in the respiratory system which will limit the side effects)	
Pharmaco-dynamics	• Inhibit bronchoconstriction and mucus secretion. • Less effective than β2-agonists. • No anti-inflammatory action only bronchodilator	
Uses	• **Main choice in chronic obstructive pulmonary diseases (COPD).** • In asthma combined with β2 agonists and corticosteroids. In acute severe asthma combined with β2 agonists & corticosteroids. (They both are bronchodilators with different mechanism of action, but in patients with (COPD) β2 agonists can't relief the, so we have to add other medications (either Anti-muscarinics or corticosteroids) • Never use as a rescue medication. Since it has delayed response and it is less effective than β2-agonists	
Side effects	• **dryness of mouth** (parasympathomimetic Antimuscarinic side effects) Antimuscarinics have other side effects, but since it is given by inhalation the only prominent ADR is dryness of the mouth	

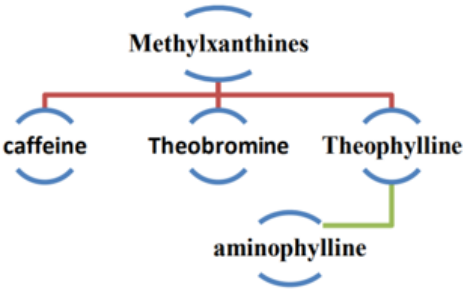
3. Methylxanthines (Theophylline - aminophylline)

Mechanism of Action

1. Phosphodiesterase inhibitors → ↑ cAMP → bronchodilation

(Phosphodiesterase is the enzyme that convert cAMP into 3,5,AMP and the inhibition of it will increase the cAMP and this is the main mechanism of action)

1. Adenosine receptors antagonists (A1) → bronchial smooth muscle relaxation
2. Increase diaphragmatic contraction
3. Stabilization of mast cell membrane



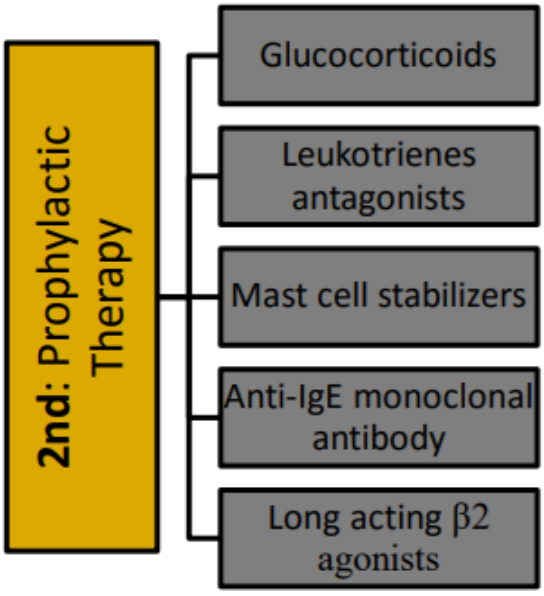
	Pharmacological effects:	Side Effects
Respiratory system	• Bronchial muscle relaxation • ↑ contraction of diaphragm → improve ventilation	**Low therapeutic index:** **(narrow safety margin)** Therefore, monitoring of theophylline blood level is necessary.
Kidney	• ↑ renal blood flow, weak diuretic action	
GIT	• ↑ gastric acid secretions = #peptic ulcer	nausea & vomiting
CVS	• ↑ heart rate (tachycardia) • ↑ force of contraction	hypotension, arrhythmia.
CNS	• stimulant effect on respiratory center. • decrease fatigue & elevate mood. All effects are similar to caffeine's	Overdose: tremors, nervousness, insomnia, convulsion

Pharmacokinetics :

- Metabolized by Cytochrome P450 enzymes in liver (All drugs metabolized by Cyt P450 must have drug drug interactions)
- T ½= 8 hours, this half-life may change depending on drug interaction
- **Drug interactions:**
  - **Enzyme inducers:**
    - As phenobarbitone & rifampicin → ↑ metabolism of theophylline → ↓ T ½.
  - **Enzyme inhibitors:**
    - as erythromycin →↓ metabolism of theophylline → ↑ T ½.

Methylxanthines	
Theophylline	**Aminophylline**
given orally	Salt derivative of theophylline, given as slow infusion
Second line drug in asthma	Used for status asthmatics (severe form of asthma)

Prophylactic Therapy



(control medications/prophylactic therapy/ Anti-inflammatory drugs) effects:

- ↓ bronchial hyper-reactivity.
- ↓ reduce inflammation of airways
- ↓ reduce the spasm of airways

Glucocorticoids

Mechanism of action:

Anti-inflammatory actions:

- Inhibition of phospholipase A2 (inhibiting arachidonic acid degradation pathway)
- ↓ 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 β2 receptors (have additive effect to β2 agonists).

Pharmacological actions of glucocorticoids :

- **Anti-inflammatory actions**
- **Immunosuppressant effects**
- **Metabolic effects :**
  - Hyperglycemia
  - ↑ protein catabolism
  - ↓ protein anabolism
  - Stimulation of lipolysis - fat redistribution
- **Mineralocorticoid effects:**
  - sodium/fluid retention
  - Increase potassium excretion (hypokalemia).
  - Increase blood volume (hypertension).
- **Behavioral changes:** depression.
- **Bone loss (osteoporosis)** due to :
  - Inhibit bone formation
  - ↓ calcium absorption from GIT.

Routes of administration:

- Inhalation:

Given by inhalation (metered-dose inhaler).

Have first pass metabolism and they're the best choice in asthma, less side effects

(Budesonide & Fluticasone, beclomethasone)

- Orally:

(Prednisone, methyl prednisolone)

- Injection:

(Hydrocortisone, dexamethasone)

Glucocorticoids in asthma

- Are not bronchodilators 
- Reduce bronchial inflammation 
- Reduce bronchial hyper-reactivity to stimuli 
- Have delayed onset of action (effect usually attained after 2-4 weeks).
- Maximum action at 9-12 months.
- Given as prophylactic medications, used alone or combined with β2 agonists.
- Effective in allergic, exercise, antigen and irritant-induced asthma .

Systemic corticosteroids are reserved for:

Status asthmaticus (i.v).

nhaled steroids should be considered for adults, children with any of the following features:

- using inhaled β2 agonists three times/week
- symptomatic three times/ week or more; or waking one night/week.

Clinical Uses of glucocorticoids

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

Side effects due to systemic corticosteroids :

- Adrenal suppression
- Growth retardation in children
- Susceptibility to infections 
- Osteoporosis 
- Fluid retention, weight gain, hypertension
- Hyperglycemia
- Fat distribution
- Cataract
- Psychosis

Inhalation has very less side effects:

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

Washing mouth after inhalation will decrease the side effect

Withdrawal of systemic corticosteroids :

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

Mast cell stabilizers

Clinical Uses of glucocorticoids :

e.g. Cromoglycate – Nedocromil

- given by inhalation (aerosol, nebulizer).
- Have poor oral absorption (10%). Its good thing because we just need it in respiratory system

Mechanism of action:

- act by stabilization of mast cell membrane > ↓ release of inflammatory mediators > ↓ Inflammation > ↓ Bronchospasm .

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:

حليب نيدو (Nedo) والجلي (Gly) والكريم كراميل (Cromo cromil) كلها يحبونها الأطفال غالباً

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

Side effects :

- ✓ Bitter taste. (طعمه مر)
- ✓ minor upper respiratory tract irritation (burning sensation, nasal congestio

Leukotrienes antagonists

Leukotrienes :

synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells).

- produced by the action of 5-lipoxygenase on arachidonic acid.

Leukotriene B4: chemotaxis of neutrophils

Cysteinyl leukotrienes C4, D4 & E4.

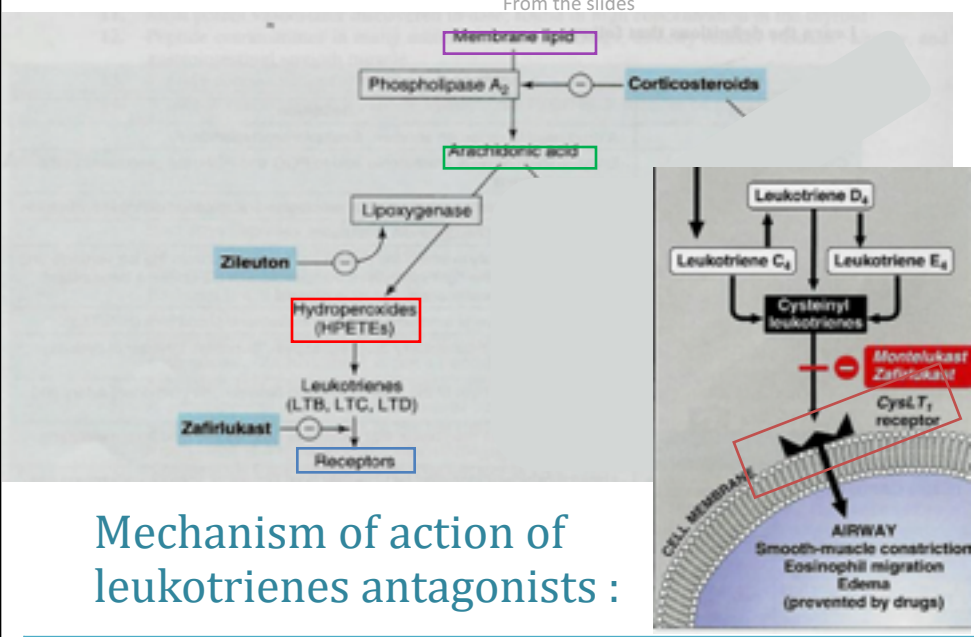
- bronchoconstriction
- increase bronchial hyper-reactivity
- ↑ mucosal edema, ↑ mucus secretion

كأنها تمشي قدام النيوترفل عشان تدلها وين مكان الانفلاميشن وتقول انا قبلك Before (B4) you

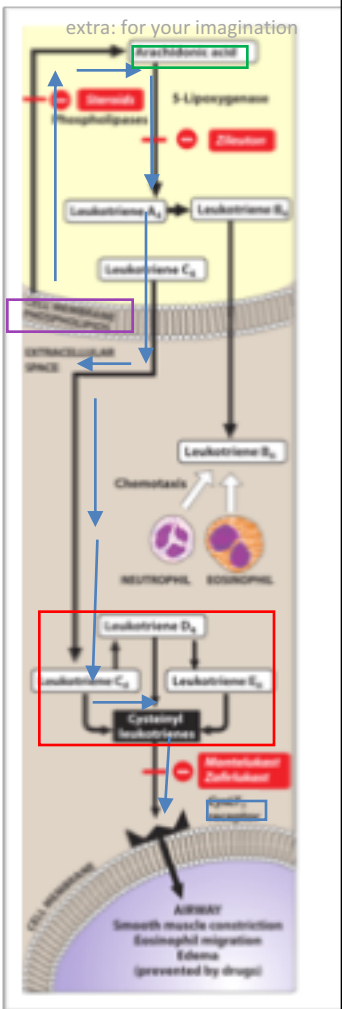
نقراها سدي (CDE) فنتذكر انها تسد مجرى الهواء وتسوي(Bronchoconstriction)

Pharmacodynamics:

From the slides



extra: for your imagination



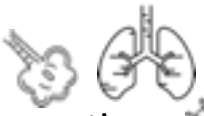
Mechanism of action of leukotrienes antagonists :

Zafirlukast	**selective, reversible antagonists (blocking) of cysteinyl leukotriene receptors (CysLT$_1$receptors)*.**
Montelukast	
Pranlukast	

Luk = Leukotriene = lock or block the receptor

Leukotrienes antagonists cont.

Leukotriene receptor antagonists :

- Taken orally. 
- Are bronchodilators 
- Have anti-inflammatory action 
- Less effective than inhaled corticosteroids.
- Have glucocorticoids sparing effect.

Uses of leukotriene receptor antagonists

- **Not** effective in acute attack of asthma.
- **Prophylaxis** of mild to moderate asthma.
- Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).

aspirin	antigen and exercise
induced asthma	

Side effects :

Elevation of liver enzymes  , headache  , dyspepsia

Anti-IgE monoclonal antibody

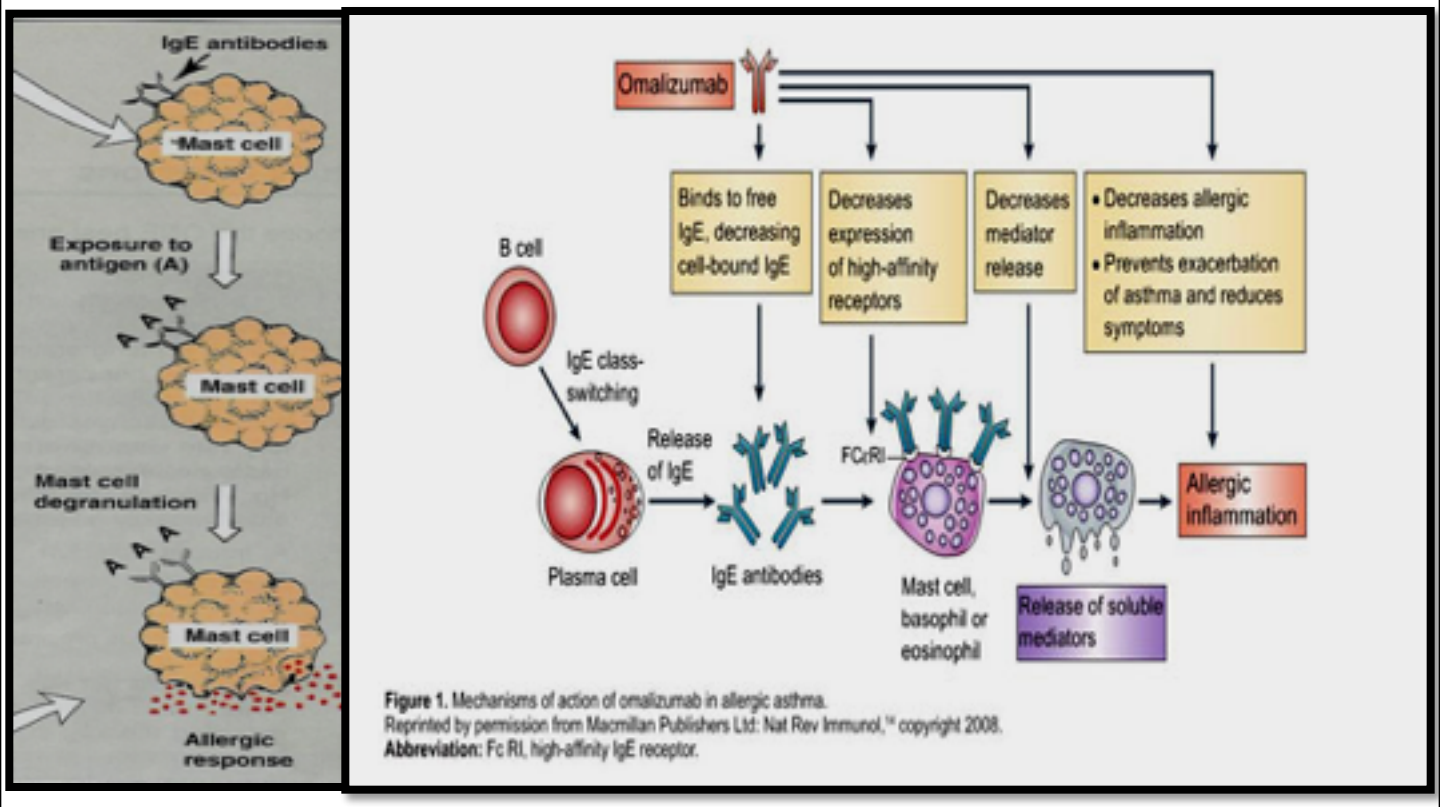
e.g. Omalizumab

- is a monoclonal antibody directed against human IgE – given by injection (s.c.)
- prevents IgE binding with its receptors on mast cells & basophiles.
- ↓ release of allergic mediators.
- Expensive-not first line therapy.
- used for treatment of moderate to severe allergic asthma which does not respond to high doses of corticosteroids.

We cant use it orally because it is a protein ,so it will destroy easily before giving its effect

Anti-IgE monoclonal antibody cont.

وظيفته انه يمنع ال IgE antibodies من الارتباط في الماست سيل عشان يقلل ال allergic response



COPD

Drugs used in chronic obstructive pulmonary disease (COPD)

- **COPD** is **a chronic irreversible (no complete recovery)** airflow obstruction, lung damage and inflammation of the air sacs (alveoli).
- COPD is characterized by chronic bronchitis and emphysema (destruction of walls of alveoli.

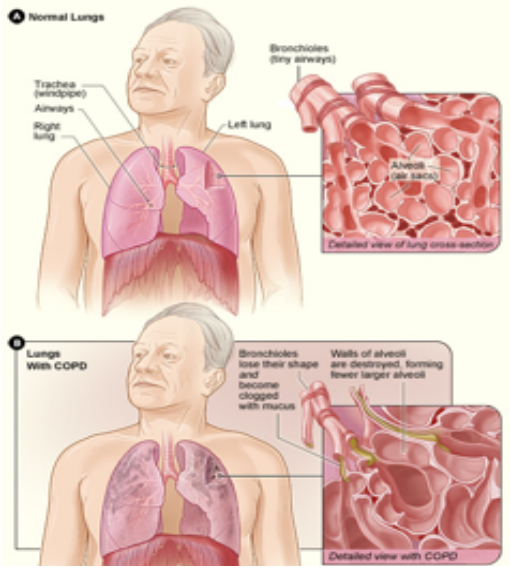
- Smoking is a high risk factor but air pollution and genetic factors can contribute.

COPD cont.

Treatment:

- Antibiotics specifically macrolides such as **azithromycin** to reduce the number of exacerbations.

- Inhaled bronchodilators .
- Inhaled glucocorticoids .
- Oxygen therapy .
- Lung transplantation



Inhaled bronchodilators in COPD :

- Inhaled antimuscarinics

- Ipratropium & tiotropium .
- are superior to β2 agonists in COPD .

- β_2 agonists (these drugs can be used either alone or combined)

- salmeterol + Tiotropium (long acting-less dose frequency).
- salbutamol + ipratropium

COPD cont.

Bronchodilators (relievers for bronchospasm)

Drugs		
B2 agonists Salbutamol, terbutaline	– Short acting – main choice in acute attack of asthma – Inhalation	↑Adenyl cyclase ↑ cAMP
Salmeterol, formoterol	Long acting, Prophylaxis Nocturnal asthma	
Antimuscarinics Ipratropium (Short) Tiotropium (long)	Main drugs For COPD Inhalation Inhalation	Blocks M receprtors
Xanthine derivatives Theophylline Aminophylline	(orally) (parenterally)	Inhibits phosphodiesterase ↑ cAMP

Anti-inflammatory drugs (prophylactic)

Corticosteroids (Inhibits phospholipase A2) Dexamethasone, Fluticasone, budesonide	Inhalation
prednisolone	Orally
Hydrocortisone	parenterally
Mast stabilizers Cromoglycate (Cromolyn), Nedocromil	Inhalation, prophylaxis in children
Cysteinyl antagonists (CyLT1 antagoist) Zafirlukast, montelukast	orally
Omalizumab (Anti IgE antibody)	Injection, SC

MCQs

1. A child suffering from asthma is to be treated with a drug that blocks the synthesis of leukotrienes. What drug would be an appropriate choice?
A. Theophylline
B. Montelukast
C. Ipratropium
D. Zileuton

2. When used in the management of asthma, glucocorticoids are likely to cause
A. hypoglycemia
B. decreases in blood pressure
C. anabolic actions in wound healing
D. oral thrush

3. Cromoglycate useful in many patients with asthma because it
A. inhibits COX 2
B. blocks adenosine receptors in bronchiolar smooth muscle
C. prevents antigen-induced degranulation of mast cells
D. inhibits phosphodiesterase

4. A 10-year-old child has severe asthma and was hospitalized
5 times between the ages of 7 and 9. He is now receiving outpatient medications that have greatly reduced the frequency of severe attacks. Which of the following is most likely to have adverse effects when used daily over long periods for severe asthma?
A. Albuterol by aerosol
B. Beclomethasone by aerosol
C. Ipratropium by inhaler
D. Prednisone by mouth

5-6. A 16-year-old patient is in the emergency department receiving nasal oxygen. She has a heart rate of 125 bpm, a respiratory rate of 40 breaths/min, and a peak expiratory flow <50% of the predicted value. Wheezing and rales are audible without a stethoscope.

5. Which of the following drugs does *not* have a direct bronchodilator effect?
A. Epinephrine
B. Ipratropium
C. Prednisone
D. Theophylline

5. Which of the following drugs does *not* have a direct bronchodilator effect?
A. Epinephrine
B. Ipratropium
C. Prednisone
D. Theophylline

6. After successful treatment of the acute attack, the patient was referred to the outpatient clinic for follow-up treatment for asthma. Which of the following is *not* an established prophylactic strategy for asthma?
A. Avoidance of antigen exposure
B. Blockade of histamine receptors
C. Blockade of leukotriene receptors
D. IgE antibody blockade

7. A 22-year-old man is brought to the emergency department after suffering seizures resulting from an overdose of a drug he has been taking. His friends state that he took the drug orally and sometimes had insomnia after taking it. Which of the following is a direct bronchodilator that is most often used in asthma by the oral route and is capable of causing insomnia
and seizures?
A. Theophylline
B. Ipratropium
C. Prednisone
D. Epinephrine

8. Which of the following in its parenteral form is life-saving in severe status asthmaticus and acts, at least in part, by inhibiting phospholipase A2?
A. Aminophylline
B. Epinephrine
C. Ipratropium
D. Prednisone

MCQs

9. Which of the following has a slow onset but long duration of action and is always used in combination with a corticosteroid by inhalation?

A. Aminophylline
B. Ipratropium
C. salbutamol
D. Zafirlukast

10. Oral medications are popular for the treatment of asthma in children because young children may have difficulty with the proper use of aerosol inhalers. Which of the following is an orally active inhibitor of leukotriene receptors?

A. Albuterol
B. Aminophylline
C. Ipratropium
D. Montelukast

11. A 34-year-old man with a long history of asthma is referred to a pulmonologist. The physician decides to prescribe zileuton. The mechanism of action of this drug is to

A. antagonize LTD4receptors
B. inhibit 5-lipoxygenase
C. inhibit phosphodiesterase
D. inhibit phospholipase

12. A 12-year-old girl with a childhood history of asthma complained of cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became so severe that her parents brought her to the emergency room. Which of the following is the most appropriate drug to rapidly reverse her bronchoconstriction?

A. Inhaled fluticasone.
B. Inhaled beclomethasone.
C. Inhaled salbutamol.
D. Oral theophylline.

SAQ

Q1) What is the mechanism of action for sympathomimetic bronchodilators?

Q2) What is the Mechanism of action for omalizumab?

Q3) What are the two categories of specific B2 agonists?

Answers:

1-D	2-D
3-C	4-D
5-C	6-B
7-A	8-D
9-C	10-D
11-B	12-C

1. They increase levels of cAMP to cause bronchodilation Less important: some inhibitory effect on release of mediators from mast cells and inhibit some microvascular permeability, as well as promote a small degree of mucociliary transport
2. Omalizumab binds to IgE and prevents IgE-instigated release of inflammatory mediators (thus decreasing the allergic response).
3.
   - short acting beta 2 agonist (rescue medications for asthma)
   - Long acting beta 2 agonist (control -medications for asthma).

Good Luck & Thank you!

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