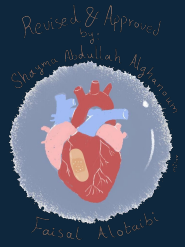


PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

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.

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

helpful video

Editing file

Bronchial 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).

Characters of airways in asthmatic patients

1

Airway hyperreactivity

Abnormal sensitivity of the airways to any external stimuli.

2

Bronchospasm

Constriction of the bronchial smooth muscles.

3

Inflammation

- Edema, swelling
- Thick mucus production.

Hyper -reactivity results into release of endogenous inflammatory mediators.
E.g. histamine, leukotrienes
*by antigen-antibody reaction (IgE)

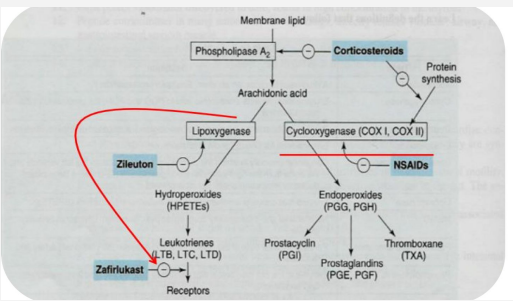
Different immunoglobulin is present in asthmatic patients

Causes of Asthma

Asthma triggers

- Infection
- Stress
- Exercise (cold air)
- Pets
- Seasonal changes
- Emotional conditions
- Some drugs as aspirin, β-bockers

From 438: Aspirin is NSAID that inhibit cyclooxygenase enzyme, so most of arachidonic acid will be converted through 5-lipoxygenase to leukotrienes instead which causes bronchoconstrictors



• Symptoms of asthma

Asthma produce recurrent episodic attack of:

1. Acute bronchoconstriction
2. Shortness of breath
3. Chest tightness
04. Wheezing
05. Rapid respiration
06. Cough

➢ Symptoms can happen each time the airways are irritated by inhaled irritants (irritants can be endogenous or exogenous) or allergens

Asthma drugs targets:

Parasympathetic supply

M3 receptors in smooth muscles and glands.

- Bronchoconstriction
- Increasing mucus secretion.

No sympathetic supply

But **β2** receptors in smooth muscles and glands

- Bronchodilation
- decreasing mucus secretion.

Anti asthmatic drugs

Bronchodilators

(Quick relief medications)
*to relieve acute episodic attacks of asthma

- Short acting β2-agonists
  Only β2 agonists (Selective) used to reduce the side effects
- Antimuscarinic
  (Atropine substitutes)
- Xanthine preparations

Anti-inflammatory Agents

(prophylactic therapy)
Control therapy to reduce the frequency of attacks, and nocturnal awakenings.

- Corticosteroids
  The most potent anti-inflammatory drugs
- Mast cell stabilizers
  To stop the release of histamine
- Leukotrienes antagonists
- Anti-IgE monoclonal antibody
- Long acting β2-agonist

NOTE: long acting beta2 agonist is a bronchodilator (not anti-inflammatory) but is NEVER used for acute attacks, it's used as a control medication and is given with corticosteroids

• Bronchodilators

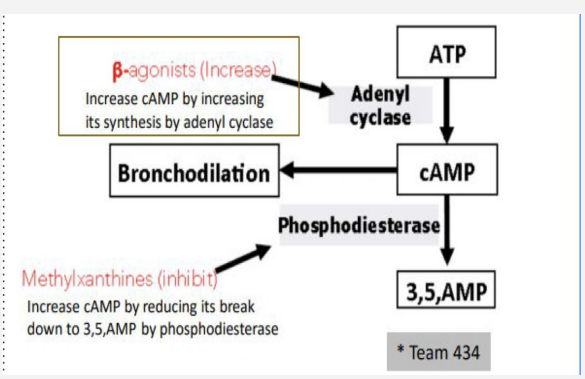
Sympathomimetics B-adrenoceptor agonist:

Mechanism of action :

- ❖ Direct B2 stimulation ⟶ Stimulate adenyl cyclase ⟶ ↑ cAMP (a second messenger comes from ATP, bronchodilator, vasodilator) Bronchodilation.
- ❖ Increase mucus clearance by (increasing ciliary activity).

(they have adrenergic receptors which upon their activation ↑ intracellular calcium, which ↑ ciliary activity).

- ❖ Stabilization of mast cell membrane (therefore reducing histamine release).



1- Non selective B-Agonist

DRUG	EPINEPHRINE (ADRENALINE)	ISOPRENALINE
CLINICAL USES	• Potent Bronchodilator • Adrenaline is the drug of choice for acute anaphylaxis (hypersensitivity reaction)	
PHARMACO KINETICS	• Given subcutaneously, S.C. Not effective orally. • Rapid onset of action (maximum effect within 15 min) • Has a short duration of action (60-90 min)	Any drug that can affect the heart is given S.C not I.V to reduce the side effects on the CVS
ADRs	• Hyperglycemia • Skeletal muscle tremor • CVS side effects: tachycardia, Arrhythmia, hypertension	
CONTRA-INDICATIONS	• CVS patient • Diabetic patients • Asthmatic patients with hypertension or heart failure.	

2- selective B2 Agonist (Preferable)

Mainly given by inhalation by: metered dose inhaler or nebulizer

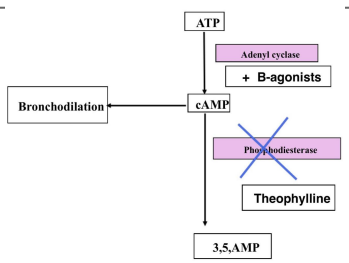
	Short acting B2 Agonist	Long acting B2 Agonist
DRUGS	• **SALBUTAMOL (ALBUTEROL)**: given by Inhalation, orally, I.V. • **TERBUTALINE**: given by inhalation, orally, S.C.	• **SALMETROL** • **FORMETROL** Both are given by inhalation End with metrol متر يعني طوويل
CLINICAL USES	• Used for acute attack of asthma (drug of choice)	• Not used to relieve acute attacks of Asthma. • Used for nocturnal Asthma. • Dr's note: Combined with inhaled Corticosteroids to control Asthma, such as (formoterol + Budesonide) to decrease the number and severity of Asthma attacks.
PHARMACO KINETICS	• Have a rapid onset action (15-30 min). • Short duration of action (4-6 hr).	• Long acting Bronchodilators (12 hr) due to high lipid solubility (creates depot effect).
Advantages	• Minimal CVS side effects. • Suitable for Asthmatic patients with CV disorders as hypertension or heart failure.	
Disadvantages	• Skeletal muscle tremors (A common characteristic. Activation of adrenergic receptors on skeletal muscles →hypokalemia → tremors) • Nervousness. • Tolerance (B-receptor down regulation). Normally receptors are internalized into the cell to be recycled, repeated use can decrease the number of receptors beyond recycling • Overdose may produce tachycardia due to B1 stimulation.(losing selectivity)	

Muscarinic Antagonist (second choice)

Drugs	Ipratropium	Tiotropium
Duration	Short duration of action (3-5) h	Longer duration of action (24) h
MOA	Act by blocking muscarinic receptor,, (non-selective)	
Pharmacodynamics	• Inhibit bronchoconstriction and mucus secretion. • Less effective than B2-Agonist. • No anti inflammatory action, only bronchodilator. • Does not enter CNS.	
Uses	• **Main drug in COPD**. • In acute severe asthma combines with B2- Agonists & Corticosteroids.(additive) • Never use as rescue medication	
PHARMACOKINETICS	• Given by Aerosol inhalation. • Have a delayed onset of action. • Not used as rescue medication.	
Other characteristics	• Quaternary derivatives of Atropine (polar). • Have minimal systemic side effect.	

Methylxanthines (Xanthine preparations) مثل القهوة

DRUG	Theophylline	Aminophylline
M.O.A.	• are phosphodiestrase inhibitors: ↑ cAMP → bronchodilation • Adenosine receptors antagonists(A1). (one of the actions that adenosine does is bronchoconstriction, so blockade of adenosine leads to bronchodilation.) • Increase diaphragmatic contraction • Stabilization of mast cell membrane	

PHARMACOLOGICAL EFFECTS	• Bronchial muscle relaxation
	• ↑contraction of diaphragm → improve ventilation.
	• **CVS**: ↑ heart rate, ↑ force of contraction
	• **GIT**: ↑ gastric acid secretions (contraindicated in patients with peptic ulcers)
	• **Kidney**: ↑renal blood flow, weak diuretic action (مايستخدم كمدر للبول)
	• **CNS stimulation**:
	  ○ stimulant effect on respiratory center.
	  ○ decrease fatigue & elevate mood.
	  ○ Overdose: tremors, nervousness, insomnia, convulsion.
		

ADMINISTRATION	Given orally	Given as slow infusion
PHARMACOKINETICS	• T ½= 8 hours • metabolized by Cyt P450 enzymes in liver . • has many drugs interactions: • Cyt P450 **Enzyme inducers** (phenobarbitone & rifampicin): ↑ metabolism of theophylline → ↓ T ½. • Cyt P450 **Enzyme inhibitors** (erythromycin): ↓ metabolism of theophylline → ↑ T ½.	
USES	Second line drug in asthma	For status asthmaticus
SIDE EFFECTS	Low therapeutic index **(narrow safety margin)** monitoring of theophylline blood level is necessary. • **GIT effects**: nausea & vomiting • **CVS effects**: hypotension, arrhythmia. • **CNS side effects**: tremors, nervousness, insomnia, convulsion.	

Anti-inflammatory drugs

Anti- inflammatory drugs include:

- **Glucocorticoids**
- **Leukotrienes antagonist**
- **Mast cell stabilizers**
- **Anti-IgE monoclonal antibody**, eg. Omalizumab.

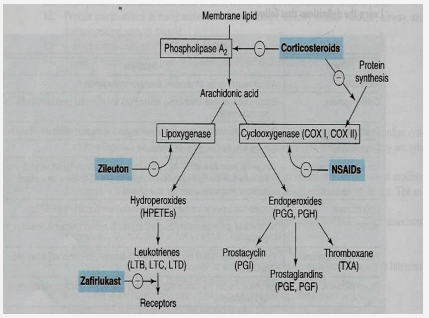
They are control medications / prophylactic therapy act by:

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

GLUCOCORTICOIDS

M.O.A.

- 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 β_2 receptors** (have additive effect to
- B_2 agonists). *this means that glucocorticoids increase the effect of β_2 agonists.



GLUCOCORTICOIDS IN ASTHMA

- Are **not** bronchodilators
- Reduce bronchial inflammation
- Reduce bronchial hyperreactivity to stimuli
- Maximum action at 9-12 months.
- Effective in allergic, exercise, antigen and irritant induced asthma .
- Have delayed onset of action (**effect usually attained after 2-4 weeks**).
- Given as prophylactic medications, used alone or combined with β_2 agonists.

ADMINISTRATION

Inhalation:

- Given by inhalation (metered-dose inhaler).
- Have first pass metabolism therefore less side effects because if some of the drug reached the esophagus it will be metabolized immediately by the liver
- Best choice in prophylaxis of asthma. e.g. **Budesonide** & **Fluticasone**, **beclometasone**.
- **Orally**: Prednisone, methyl prednisolone. (For acute asthma attack)
- **Injection**: Hydrocortisone, dexamethasone.

CLINICAL USES

- Treatment of inflammatory disorders (asthma, rheumatoid arthritis).
- Treatment of autoimmune disorders (ulcerative colitis, psoriasi) and after organ or bone marrow transplantation as immunosuppressants.
- Antiemetics in cancer chemotherapy.

Cont...

GLUCOCORTICOIDS

PHARMACOLOGICAL ACTION	• Anti-inflammatory actions
	• Immunosuppressant effects *in case of transplantation, so that tissue rejection doesn't happen.
	• **Metabolic effects** :
	  ○ Hyperglycemia
	  ○ ↑ protein catabolism,↓ protein anabolism
	  ○ Stimulation of lipolysis (fat redistribution).
	• **Mineralocorticoid effects:**
	  ○ sodium/fluid retention
	  ○ ↑ potassium excretion (hypokalemia)
	  ○ ↑ blood volume (hypertension)
	• Behavioral changes: depression
	• Bone loss (osteoporosis) due to:
	  ○ Inhibit bone formation
	  ○ ↓ calcium absorption from GIT.

• Side effects due to systemic corticosteroids:

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

❑ **Systemic corticosteroids are reserved for:**

Status asthmaticus (i.v.).

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

I. using inhaled β_2 agonists three times/week
II. symptomatic **three times**/ week or more;
III. or waking **one night**/week.

❑ **Inhalation has very less side effects, but can cause:**

- Oropharyngeal candidiasis (thrush).fungal infection by Candida species caused by the suppression of normal flora and the pathogen
- Dysphonia (voice hoarseness) Rinse properly to reduce these effects.

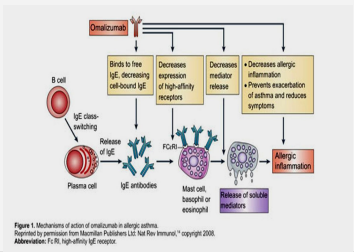
❑ **Withdrawal of systemic corticosteroids**

Abrupt stop of corticosteroids should be avoided and dose should be tapered (to avoid **adrenal insufficiency syndrome**). Administration and withdrawal should be gradual

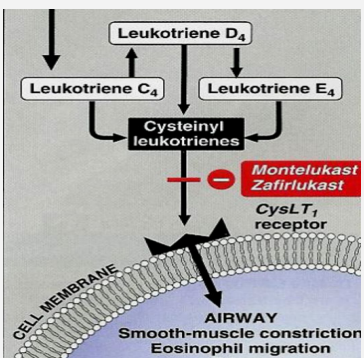
Mast cell stabilizers

Drugs	Cromoglycate (cromolyn)	Nedocromil mnemonic from our greatest academic leader نيدو بالكراميل
M.O.A and pharmacodynamics	● act by stabilization of mast cell membrane. ● They are not bronchodilators, so they are not effective in acute attack of asthma . ● Prophylactic anti-inflammatory drugs . ● Reduce bronchial hyperreactivity .”No histamine = no inflammation “ ● Effective in exercise, antigen and irritant-induced asthma. ● Children respond better than adults.	
Uses	● Prophylactic therapy in asthma especially in children. ● Allergic rhinitis . ● Conjunctivitis.	
Pharmacokinetics	● given by inhalation (aerosol, nebulizer). ● Have poor oral absorption (10%).	
Side effects	● Bitter taste ● minor upper respiratory tract irritation (burning sensation,nasal congestion) Due to it’s powder form	

Anti-IgE monoclonal antibody

Drugs	Omalizumab
M.O.A and pharmacodynamics	● a monoclonal antibody directed against human IgE . ● prevents IgE binding with its receptors on mast cells & basophiles. ● Decrease the release of allergic mediators.(IgE) 
Uses	● used for treatment of moderate to severe allergic asthma which does not respond to high doses of corticosteroids.	
Pharmacokinetics	● given by injection (s.c.)	
Disadvantages	● Expensive-not first line therapy.	

Leukotrienes antagonists

Drugs	Zafirlukast	Montelukast	Pranlukast
M.O.A and pharmacodynamics	• selective, reversible antagonists of cysteinyl leukotriene receptors (CysLT1 receptors). • bronchodilators "but have delayed onset of action " • Have anti-inflammatory action • Less effective than inhaled corticosteroids. • Have glucocorticoids sparing effect (potentiate corticosteroid actions). (Corticosteroids أعطيه معاه عشان اقلل جرعة)		
Uses	• Prophylaxis of mild to moderate asthma (e.g. aspirin-induced asthma, antigen and exercise-induced asthma) • **Not** effective in acute attack of asthma. • Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).		
Pharmacokinetics	• Taken orally.		
Side effects	• Elevation of liver enzymes, headache, dyspepsia		
Target	Leukotrienes: inflammatory mediators synthesized by inflammatory cells found in the airways (eosinophils, macrophages, mast cells) , and produced by the action of 5-lipoxygenase on arachidonic acid. Examples of Leukotrienes: • Leukotriene B4: chemotaxis of neutrophils. • Cysteinyl leukotrienes C4, D4 & E4: bronchoconstriction ↑ bronchial hyperreactivity ↑ mucosal edema and mucus secretion		

Drugs used in chronic obstructive pulmonary disease (COPD)

COPD is a chronic irreversible airflow obstruction, lung damage and inflammation of the air sacs (alveoli).

COPD

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.

- **Treatment**:

Supportive therapy only, it can't repair what has been damaged

- ❖ Antibiotic specifically macrolides such as **azithromycin** to reduce the number of exacerbations
- ❖ Lung transplantation
- ❖ Inhaled bronchodilators
- ❖ Inhaled glucocorticosteroids
- ❖ Oxygen Therapy

Inhaled bronchodilators in COPD

β2 agonists

- **These drugs can be used alone or combined :**

➢ Salbutamol + ipratropium
➢ Salmeterol + tiotropium. (long acting-less dose frequency)

Inhaled antimuscarinics

➢ Ipratropium & tiotropium
➢ Are superior to **β2** agonists in COPD

Summary for drugs used in Asthma

Bronchodilators (relievers for bronchospasm)			
Drugs		characteristic	target
β2 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	• Block M receptors
Xanthine derivatives	Theophylline aminophylline	- Orally - Parenterally	• Inhibits phosphodiesterase • ↑ cAMP

Anti-inflammatory drugs (prophylactic)		
Drugs		Mode of administration
Glucocorticoids (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
Anti IgE antibody	Omalizumab	Injection (SC)

MCQ

1-which of the following is a prophylactic drug?			
A- β2 agonists	**B-** Antimuscarinics	**C-**Xanthine derivatives	**D-**Anti IgE antibody

2-which drug is used for status asthmaticus cases?			
A-Mast cell stabilizer	**B-Leukotrienes antagonist**	**C-Sympathomimetics**	**D-Glucocorticoids**

3-A 68-year-old man has COPD with moderate airway obstruction. Despite using salmeterol twice daily, he reports continued symptoms of shortness of breath with mild exertion. Which agent is an appropriate addition to his cument therapy?			
A-Glucocorticoids	**B-**Tiotropium	**C-**Salbutamol	**D-**Theophylline

4-12-year-old girl with asthma presents to the emergency room with complaints of cough, dyspnea, and wheezing after visiting a riding stable. Which is the most appropriate drug to rapidly reverse her bronchoconstriction?			
A-Salbutamol	**B-**Dexamethasone	**C-**Zafirlukast	**D-**Tiotropium

5- inhaled bronchodilator used superiorly for COPD?			
A-Salbutamol	**B-**Salmeterol	**C-**Omalizumab	**D-**Ipratropium

Answers

1	2	3	4	5
D	D	B	A	D

SAQ

Q1)What is the M.O.A of Muscarinic Antagonist?

Q2)Enumerate side effects of Glucocorticoids

Q3) Name one contraindication of Non selective B-Agonist

Q4) What is the mechanism of action for sympathomimetic bronchodilators?

Q5) List three Bronchodilators:

Answers

A1) Act by blocking muscarinic receptor, where Ach binds, (non-selective)

A2) slide 8

A3) slide 5

A4) slide 4

A5) Salbutamol, Ipratropium, Theophylline.....

GOOD LUCK!

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