Lecture 4 & 5

Drugs used in Asthma and COPD

Objective :

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

- Additional Notes
- Important
- Explanation –Extra-

Bronchial Asthma

It 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).

Symptoms

- Asthma produces recurrent episodic attack of : Acute bronchoconstriction, Shortness of breath, Chest tightness, Wheezing, Rapid respiration, Cough.
- Symptoms can happen each time the airways are irritated by inhaled irritants or allergens.

Causes

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

Characters of airways

- Airway **hyper-reactivity**: abnormal sensitivity of the airways to any external stimuli.
- Inflammation: ↑ edema, swelling + ↑ Thick mucus production.
- Bronchospasm (constriction of the bronchial smooth muscles).

Airways Innervations

- Afferent nerves (sensory)
  - **Irritant receptors** in upper airways.
  - **C-fiber receptors** in lower airways.
- Efferent nerves (motor nerves)
  - Parasympathetic supply M3 receptors in smooth muscles and glands: Bronchoconstriction and Increase mucus secretion.
  - No sympathetic supply but β 2 receptors in smooth muscles and glands: Bronchodilatation, Decrease mucus secretion.

We want to enhance the sympathetic or inhibit the parasympathetic in this case.

Afferent nerves (sensory) are stimulated by:

- Exogenous chemicals or irritants
- Physical stimuli (cold air)
- Endogenous inflammatory mediators e.g. histamine

1. Quick relief medications (Bronchodilators): Bronchodilators used to rapid relieve acute episodic attacks of asthma.

- Short acting β2-agonists
- Anti-muscarinic
- Xanthine preparations (this substance has effects like coffee and tea "caffeine ")

Mechanism of Action:

- Direct β_2 stimulation ⟶ stimulate adenyl cyclase ⟶ ↑ cAMP → Bronchodilatation.
- Increase mucus clearance by (increasing ciliary activity).
- Stabilization of mast cell membrane.

When cAMP increase in the cell.. Ca+ levels decrease which prevents contraction and cause Bronchodilatation.

---

2. Control therapy (prophylactic drugs): Anti-inflammatory drugs used to reduce the frequency of attacks, and nocturnal awakenings (attacks at night).

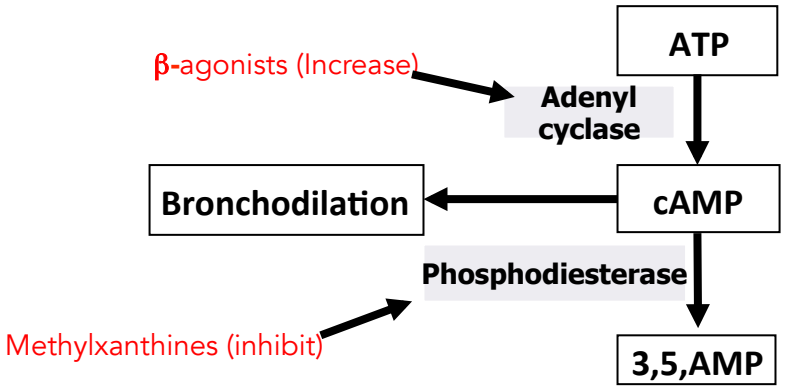
- Corticosteroids: -Given as prophylactic medications, used alone or combined with β_2 agonists.
  -Effective in allergic, exercise, antigen and irritant-induced asthma.
  -Systemic corticosteroids are reserved for: Status asthmaticus (i.v.).

Inhaled steroids should be considered for adults, children with any of the following features : using inhaled β_2 agonists three times/week , symptomatic three times/ week or more; or waking one night/week.

- Mast cell stabilizers.
- Leukotriene's antagonists
- Anti-IgE monoclonal antibody
- Long acting ß2-agonists

What do they do ?

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



Bronchodilators

These drugs can produce rapid relief of bronchoconstriction - β2 adrenoreceptor –agonists (Sympathomimetics)

Classification of β agonists	Non selective β agonists		Selective β2 – agonists (**Preferable**)			
	epinephrine	**isoprenaline**	**Salbutamol (albuterol)**	**Terbutaline**	**Salmeterol**	**Formeterol**
	Potent bronchodilator		-		-combined with inhaled corticosteroids to control asthma. (decreases the number and severity of asthma attacks).	
Duration of action	- Rapid action (maximum effect within 15 min) – different than onset of action where it works in 5 minutes - - Has short duration of action (60-90 min) – because it's natural -		Short acting ß2 agonists - Have rapid onset of action (15-30 min). - short duration of action (4-6 hr)		Long acting ß2 agonists 12 hours Bronchodilators due to **high lipid solubility** (creates depot effect).	
Administration	Given subcutaneously, S.C.		Inhalation, orally, i.v.	inhalation, orally, s.c.	Inhalation -is the preferable way in asthma-.	
Uses	**Drug of choice** for acute anaphylaxis (hypersensitivity reactions).		used for acute episodic attack of asthma (**drugs of choice**).		- not used to relieve acute episodes of asthma –because the onset of action is delayed - - used for nocturnal asthma (الربو الليلي) (**drugs of choice**).	
Dis-advantages	Non selective = many side effects - Not effective orally - will be broken down by COMT and MAO. - Hyperglycemia, Skeletal muscle tremor. **CVS side effects:** tachycardia, arrhythmia, hypertension. - Not suitable for asthmatic patients with hypertension or heart failure.		-Skeletal muscle tremors. - Nervousness - Tolerance (β -receptors down regulation) – decrease number of receptors → No response - - Overdose may produce tachycardia due to β_1 stimulation .			
Contra-indications	CVS patients, diabetic patients		-			
Advantages	-		Minimal CVS side effects and suitable for asthmatic patients with CV disorders as hypertension or heart failure.			

Bronchodilators Con.

	Anti-muscarinics		Xanthine preparations (Methylxanthines)	
Mechanism of Action	**(Muscarinic antagonists)** Act by blocking muscarinic receptors (Inhibit bronchoconstriction and mucus secretion)		- Are phosphodesterase inhibitor → increases cAMP → Bronchodilatation. –this is the main mechanism- - Universal Adenosine receptors (A1) antagonists → prevent bronchoconstriction. - Increase diaphragmatic contraction. - Stabilization of mast cell membrane.	
Classification of β agonists	Ipratropium	Tiotropium	Theophylline	aminophylline
Administration	given by aerosol inhalation → local		given orally .	is given as slow infusion .
Uses	-Main choice in chronic obstructive pulmonary diseases (COPD). -In acute severe asthma combined with β_2 agonists & corticosteroids.		Second line drug in asthma. -it is not used in Saudi Arabia and it's very cheap-.	For status asthmatics (aminophylline, is given as slow infusion).
Pharmaco-kinetics & Duration of action	-has short duration of action 3-5 hr (Have delayed onset of action)	-has longer duration of action (24 h)	-metabolized by Cyt P450 enzymes in liver -T ½= 8 hours -has many drug interactions. -**Enzyme inducers:** as phenobarbitone and rifampicin → ↑ metabolism of theophylline → ↓ ½T . **Enzyme inhibitors**: as erythromycin→ ↓ metabolism of theophylline → ↑ ½T.	
Pharmacological Effects & characterized by	Quaternary derivatives of atropine (polar) -Does not diffuse into the blood -Do not enter CNS -Less effective than β_2-agonists. -No anti-inflammatory action only bronchodilator		- Bronchial muscle relaxation -↑contraction of diaphragm → improve ventilation CVS: ↑ heart rate, ↑ force of contraction GIT: ↑ gastric acid secretions Kidney: ↑ renal blood flow, weak diuretic action CNS stimulation: - stimulant effect on respiratory center. - decrease fatigue & elevate mood.	
Disadvantages	They have slow onset of action - β2 blockers are better		-Low therapeutic index (narrow safety margin) monitoring of theophylline blood level is necessary. -CVS effects: hypotension- may lead to reflex tachycardia-, arrhythmia. -GIT effects: nausea & vomiting -CNS side effects: tremors, nervousness, insomnia, convulsion	

	Corticosteroids	Mast cell stabilizers	Leukotriene's antagonists	Anti-IgE monoclonal antibody
		Cromoglycate Nedocromil	zafirlukast montelukast pranlukast	Omalizumab
Mechanism of Action	- 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).	- 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 (Pharmacodynamics)	**Leukotriene B4:** chemotaxis of neutrophils. **Cysteinyl leukotrienes C4, D4 & E4:** - Bronchoconstriction - increase bronchial hyper-reactivity - ↑ mucosal edema. - ↑ mucus secretion.	Any drug ends with suffix (-mab) means that it deals with antibodies.. So it's a protein, and it can't be taken orally because proteins will be broken by stomach gastric.
Pharmacological actions	-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.	-	-are selective, reversible antagonists of cysteinyl leuko Taken orallytriene receptors ($CysLT_1$ receptors). -Are bronchodilators -Have anti-inflammatory action -Less effective than inhaled corticosteroids -Have glucocorticoids sparing effect (potentiate corticosteroid actions).	-is a monoclonal antibody directed against human IgE -prevents IgE binding with its receptors on mast cells & basophiles. - ↓ release of allergic mediators.

Administration	Inhalation: e.g. **Budesonide & Fluticasone, beclometasone** -Given by inhalation (metered-dose inhaler). - Have first pass metabolism -Best choice in asthma, less	- given by inhalation (aerosol, nebulizer). - Have poor oral absorption (10%)	-	given by injection (s.c.)
side effects	Orally: Prednisone, methyl prednisolone Injection: Hydrocortisone, dexamethasone	-	-	-
Duration of action	-Have delayed onset of action (effect usually attained after 2-4 weeks). -Maximum action at 9-12 months.	-	-	-
uses	-Treatment of inflammatory disorders (asthma, rheumatoid arthritis). -Treatment of autoimmune disorders (ulcerative colitis, psoriasis) and after organ or bone marrow transplantation. -Antiemetic's in cancer chemotherapy	-Prophylactic therapy in asthma especially in children. -Allergic rhinitis. -Conjunctivitis.	-Not effective in acute attack of asthma. -Prophylaxis of mild to moderate asthma. -Aspirin-induced asthma -Antigen and exercise-induced asthma -Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).	-used for treatment of moderate to severe allergic asthma which does not respond to high doses of corticosteroids
Side effects	-Adrenal suppression , Growth retardation in children, Susceptibility to infections, Osteoporosis, Fluid retention, weight gain, hypertension, Hyperglycemia, Fat distribution, Cataract, Psychosis	-Bitter taste -minor upper respiratory tract irritation (burning sensation, nasal congestion)	Elevation of liver enzymes, headache, dyspepsia	-

Drugs used in chronic obstructive pulmonary disease (COPD) :

-COPD is a chronic **irreversible** airflow obstruction, lung damage and inflammation of the air sacs (alveoli).
-Smoking is a high risk factor but air pollution and genetic factors can contribute.
Treatment: Inhaled bronchodilators, Inhaled glucocorticoids, Oxygen therapy, Antibiotics specifically macrolides such as: azithromycin to reduce the number of exacerbations, Lung transplantation.
Inhaled bronchodilators in COPD:
1-**Inhaled antimuscarinics** : pratropium & tiotropium .are superior to β 2 agonists in COPD
2-β **2 agonists:** these drugs can be used either alone or combined: salbutamol + ipratropium Or salmeterol + Tiotropium (long acting-less dose frequency).

Summary

1. Quick relief medications (Bronchodilators):

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

2. Control therapy (prophylactic drugs):

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	orally
Omalizumab (**Anti IgE antibody**)	Injection, SC

MCQs

1. Drug of choice for acute anaphylaxis?
A) Terbutaline
B) Epinephrine
C) Salbutamol
D) Formoterol

2. Which are mainly given by inhalation?
A) Selective β agonists
B) Selective β_2 agonists
C) Non selective β agonists
D) Non selective β_2 agonists

3. Which is not used to relieve acute attack of asthma?
A) Salbutamol
B) Terbutaline
C) Salmeterol
D) Albuterol

4. One of main drugs for COPD?
A) Theophylline
B) Formoterol
C) Nedocromil
D) Ipratropium

5. Increase of cAMP results in?
A) Bronchoconstriction
B) Bronchodilation
C) Stabilization of mast cell membrane
D) Increase mucus clearance

6. Which has additive effect to β_2 agonists?
A) Antimuscarinics
B) Methylxanthines
C) Glucocorticoids
D) β_2 agonists

Answers:
1- B
2- B
3- C
4- D
5- B
6- C

Good luck!

Done by Pharmacology team 434

Moneera Al draihem
Maha Al-Rabiah
Lama Al walaan
Lamia Althwadi
Rasha Bassas
Nuha AlGwaiz

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com