MED438
KING SAUD UNIVERSITY

pharmacology
Team 438

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Bronchial Asthma and COPD

- Red : important
- Black : in male / female slides
- Pink : in female's slides only
- Blue : in male's slides only
- Females doctor notes
- Grey: Males doctor notes

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.

Editing File

Bronchial Asthma:

Asthma is a chronic inflammatory disorder (Obstructive diseases) of bronchial airways that result in airway obstruction in response to external stimuli or triggers.

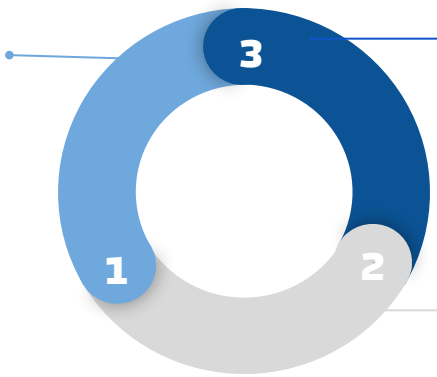
Characters of airways in asthmatic patients :

Airway hyperreactivity:

- Is an abnormal sensitivity of the airways to any external stimuli. (Different immunoglobulin is present in asthmatic patients).
- results in release of endogenous inflammatory mediators.

e.g. histamine, leukotrienes

* By antigen-antibody reaction (IgE)



Bronchospasm:

(happens due to the release of histamine & leukotriens)

- Constriction of the bronchial smooth muscles.

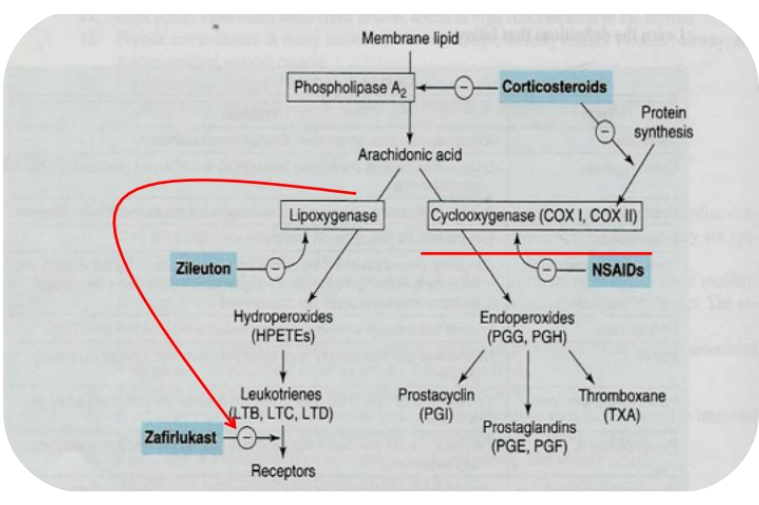
Inflammation:

- ↑ Edema, swelling.
- ↑ Thick mucus production.

2 Triggers of asthma:

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

Aspirin is NSAID which will inhibit the cyclooxygenase enzyme, so most of arachidonic acid will be converted through 5-lipoxygenase to leukotrienes instead which causes bronchoconstrictors, and they are important chemical mediators in the pathogenesis of asthma. .



3 Symptoms of asthma

Asthma produces recurrent episodic attack of :

- Acute bronchoconstriction
- Shortness of breath
- Chest tightness
- Wheezing
- Rapid respiration
- Cough (mostly it is dry)

❖ Symptoms can happen each time the airways are irritated by inhaled irritants or allergens.

Anti asthmatic drugs

Bronchodilators (Quick relief)

Treat **acute** episodic attack of Asthma.

- Antimuscarinics (Atropine substitutes)
- Short acting ß2-agonists — Only ß2 agonists (Selective) used to reduce the side effects
- Xanthine preparations

Reduce the frequency of attacks and nocturnal *night awakenings

Prophylactic (control) therapy (Anti-inflammatory)

"prophylactic means reduce the number of attack"

- Corticosteroids — The most potent anti-inflammatory drugs
- Mast cell stabilizers — To stop the release of histamine
- Leukotrienes antagonists
- Anti-IgE monoclonal antibody — stops the effect of the allergen
- Long acting ß2-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

First : Bronchodilators

For better understanding of Bronchodilators, we recommend that you familiarize yourself with the Innervations of the respiratory system

Parasympathetic supply:

-M3 receptors in smooth muscles and glands
Action:
Bronchoconstriction
+Increase mucus secretion.

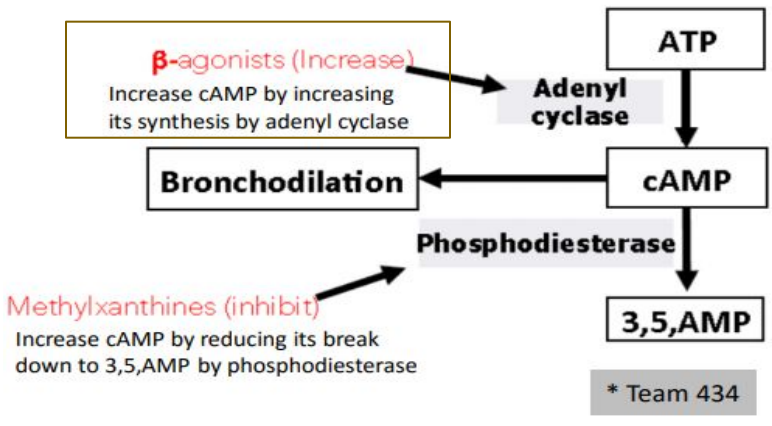
Sympathetic supply:

-B2 receptors in smooth muscles and glands.
Action :Bronchodilation
+Decrease mucus secretion.

β- adrenoceptor agonists (Sympathomimetics)

Mechanism of action for selective & Non-selective Sympathomimetics:

- **stimulate β2 Directly** → 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).



A) Non-selective β-agonist

	Epinephrine (Adrenaline)	Isoprenaline
Clinical uses	• Epinephrine: Non-selective adrenergic agonist (α1, α2, β1, β2) • Potent bronchodilator • **Adrenaline** is the drug of choice for **acute anaphylaxis** (hypersensitivity reaction) can be used for asthma BUT selective B2 are better in case of asthma.	
Pharmacokinetics	• Given S.C, I.M, inhalation Not effective orally *(any drug that can affect the heart is given S.C not I.V to reduce the side effects on the CVS). • Rapid onset of action (maximum effect within 15 min) . • Has short duration of action (60-90 min).	
ADRs	• Hyperglycemia. • Skeletal muscle tremor. • CVS side effects (β1 actions): tachycardia, arrhythmia, hypertension.	
Contra-indications	• CVS patients :hypertension, heart failure. • Diabetic patients, hyperthyroidism • Asthmatic patient with hypertension.	

B) Selective β2 agonist

Are mainly given by inhalation by: metered dose inhaler or nebulizer

	Short acting selective ß2 agonists	Long acting selective ß2 agonists
Drugs	• **Salbutamol** (albuterol) : Mainly given by inhalation, orally , I.V . • **Terbutaline** : Mainly given by inhalation, orally, s.c.	• **Salmeterol.** • **Formoterol** Are given by inhalation.
Clinical uses	• Drugs of choice for **acute episodic attack** of asthma (especially salbutamol)	• Are NOT used to relieve acute episodes of asthma. • Used for nocturnal asthma. • combined with inhaled corticosteroids to control asthma "prophylactic medication" (to decrease the number and severity of asthma attacks).
	Suitable for asthmatic patients with CV disorders as hypertension or heart failure , **due to Minimal CVS side effects .**	
Pharmacokinetics	• Have rapid onset of action (15- 30 min) • Short duration of action (4-6 hr).	• Long acting bronchodilators (12 hours) due to **high lipid solubility** (creates depot effect). increased storage of drug in the body & gradually released.
ADRs	• Skeletal muscle tremors. (A common characteristic. Activation of adrenergic receptors on skeletal muscles → hypokalemia → tremors) • Nervousness , insomnia. • Tolerance (β-receptors 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 β1 stimulation.	

Muscarinic antagonists (2nd choice)

	Ipratropium	Tiotropium
Mechanism of action	• Act by blocking muscarinic receptors (non-selective).	
Pharmacodynamics	• Inhibit bronchoconstriction and mucus secretion with no anti-inflammatory action. • Less effective than β2-agonists. • Does not diffuse into the blood . • Does not enter CNS. (No CNS Effect)	
Uses	• Main choice in chronic obstructive pulmonary diseases (COPD). • In asthma combined with β2 agonists & corticosteroids.	
Pharmacokinetics	• given by aerosol inhalation. • Have delayed onset of action. **(Never used as rescue medications)** *Short acting ß2 agonists are preferably used in cases of emergency because of the rapid onset of action.	
Duration	has short duration of action (3-5 hrs)	has longer duration of action (24 hrs)
other characteristics	- Quaternary derivatives of atropine (polar). - Have minimal systemic side effects.	

Methylxanthines (Xanthine preparations)

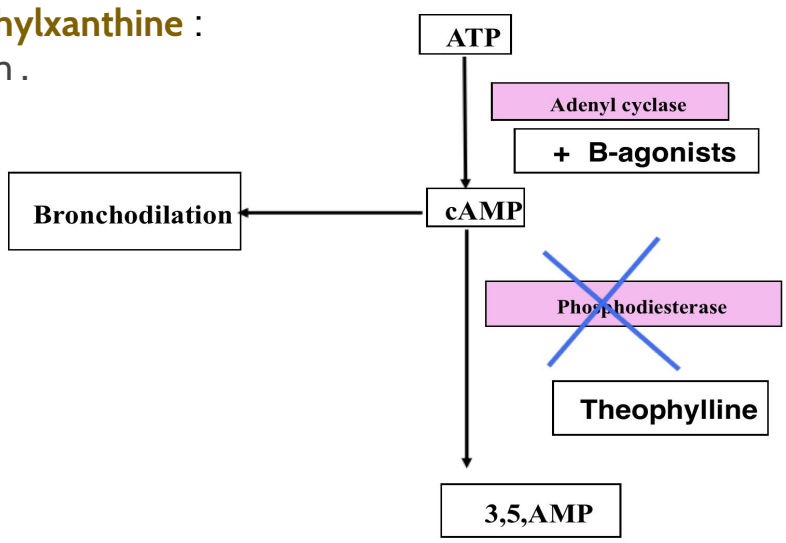
	Theophylline	Aminophylline
Mechanism of action	• are phosphodiestrase inhibitors: → cAMP →↑bronchodilation *phosphodiesterase break down cAMP →↓cAMP , so we use these drugs to inhibit phosphodiesterase) • Adenosine receptors antagonists. one of the actions that adenosine does is bronchoconstriction, 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
	• CNS stimulation:
	  ○ stimulant effect on respiratory center.
	  ○ decrease fatigue & elevate mood.
	  ○ **Overdose:** tremors, nervousness, insomnia,convulsion.	

Cont..

	Theophylline	Aminophylline
Administration	is given orally	is 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.	

β- adrenoceptor agonists vs **Methylxanthine** :
*same action different mechanism .



Second : Anti-inflammatory Agents

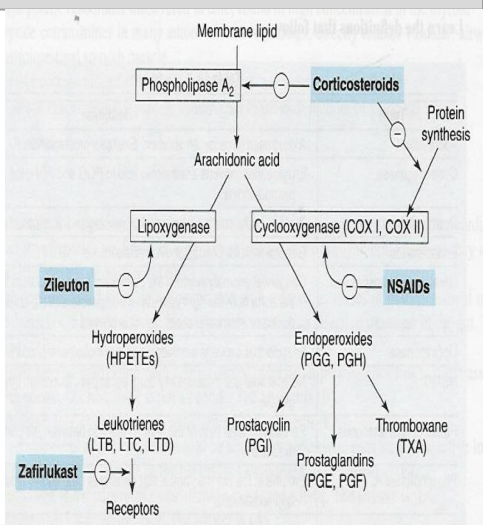
They are control medications / prophylactic therapy act by :

- ↓ **bronchial hyperreactivity.**
- ↓ **inflammation of airways**
- ↓ **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 β2 receptors** (have additive effect to B2 agonists). *this means that glucocorticoids increase the effect of β2 agonists.



Glucocorticoids in Asthma

- Are **not** bronchodilators (however they do **reverse** and provide a prophylactic effect in bronchoconstriction, and are mainly used to relieve the inflammatory effects) .
- **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 β2 agonists.

Pharmacological action

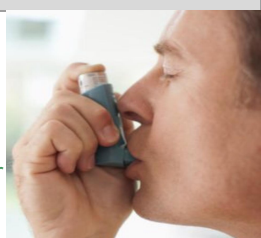
- **Anti-inflammatory actions**
- **Immunosuppressant effects** *in case of transplantation, so that tissue rejection doesn't happen.
- **Metabolic effects :** Hyperglycemia + ↑ protein catabolism + ↓ protein anabolism + Stimulation of lipolysis (fat redistribution).
- **Mineralocorticoid effects:**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

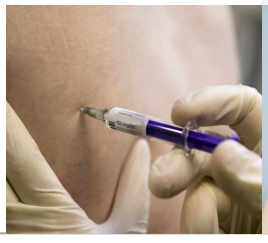
Administration

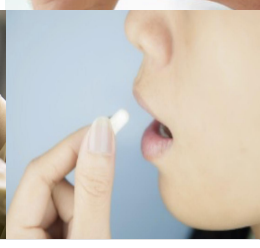
- **Inhalation:**

Given by inhalation (metered-dose inhaler).
Have first pass metabolism therefore less side effects so it's the best choice in prophylaxis of asthma.
e.g. **Budesonide & Fluticasone,beclometasone.**

because if some of the drug reached the esophagus it will be metabolized immediately by the liver







- **Orally:** Prednisone, methyl prednisolone .
- **Injection:** Hydrocortisone, dexamethasone.

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Clinical Uses of glucocorticoids

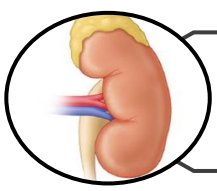
- Treatment of **inflammatory disorders** (asthma,rheumatoid arthritis).
- Treatment of **autoimmune disorders** (ulcerative colitis, psoriasis الصدفية) and after organ or bone marrow transplantation as immunosuppressants.
- **Antiemetics** in cancer chemotherapy. مضاد للقيء

- **Systemic corticosteroids are reserved for:**
  - **Status asthmaticus (i.v.)**

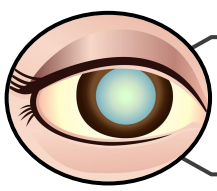
❖ Side effects due to systemic (oral or injection) corticosteroids:

Fluid Retention, Hypertension, Weight gain, Hyperglycemia

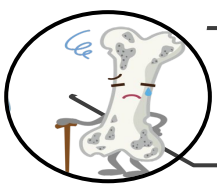
Growth retardation in children



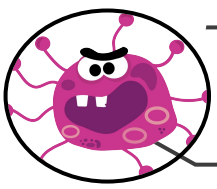
Adrenal suppression
(adrenal atrophy, most serious side effect)



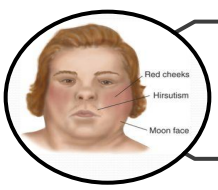
Cataract



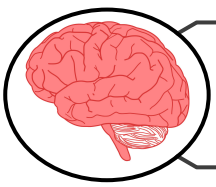
Osteoporosis



Susceptibility to infections



Fat distribution



Psychosis

❖ Inhalation has very less side effects:

but can cause the following:

- 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

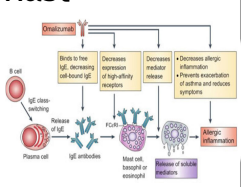
Abrupt stop of corticosteroids should be avoided and dose should be tapered (adrenal insufficiency syndrome).

Administration and withdrawal should be gradual

Mast cell stabilizers

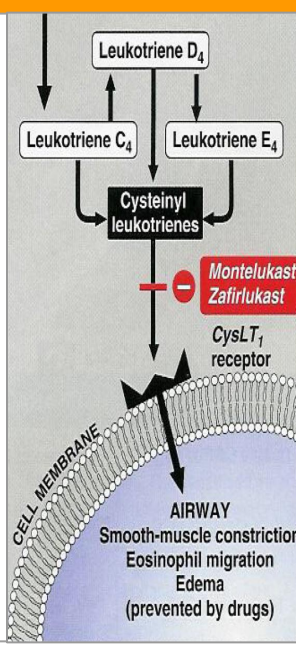
Mechanism of action and pharmacodynamics	• **act by stabilization of mast cell membrane.** • They are **not** bronchodilators, so they are **not** effective in acute attack of asthma . • Prophylactic anti-inflammatory drugs . • Reduce bronchial hyperreactivity ."No histamine = no inflammation " • Effective in exercise, antigen and irritant-induced asthma. • **Children respond better than adults.**
Examples	• **Cromoglycate (also called cromolyn) , Nedocromil**
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)

Anti-IgE monoclonal antibody

Mechanism of action 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. 
Uses	• used for treatment of **moderate to severe** allergic asthma which does not respond to high doses of corticosteroids.
Examples	• **Omalizumab**
Pharmacokinetics	• given by injection (s.c.) .
Disadvantage	• Expensive-not first line therapy.

Leukotrienes antagonists

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 and ↑ mucosal edema and mucus secretion .
Mechanism of action 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.
Examples	• **Zafirlukast , Montelukast and Pranlukast**
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).
P.K	• Taken orally.
Side effects	• Elevation of liver enzymes, headache, dyspepsia



Glucocorticoids sparing effect:
What this means is that when glucocorticoids are given with leukotrienes antagonists , we reduce the dose of glucocorticoids and therefore this will make the side effects less.

Chronic Obstructive Pulmonary Disease (COPD)

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

- 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

- **Inhaled bronchodilators**
- **Oxygen therapy**
- **Lung transplantation**
- **Inhaled glucocorticoids**
- **Antibiotics specifically macrolides such as azithromycin to reduce the number of exacerbations.**

Inhaled bronchodilators in COPD

1 Inhaled antimuscarinics

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

2 β2 agonists

-be used either alone or combined:

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

Bronchial asthma Vs COPD (from 435)

Obstructive diseases	Bronchial asthma	COPD
Definition	Chronic inflammatory disorder in bronchial airways result in airway obstruction	Chronic airflow obstruction caused by lung damage and inflammation of the air sacs (alveoli)
Causes	Exogenous agents ,stress ,cold air , exercises ,pets ,seasonal changes , emotions , some drugs(like aspirin and β-blockers)	• Smoking . • Air pollutant .
Treatment	*Bronchodilators: • Short acting beta 2-agonists • Antimuscarinics • Xanthine preparations *Prophylactic therapy: • Corticosteroids. • Mast cell stabilizers. • Leukotrienes antagonists • Anti-IgE monoclonal antibody. • Long acting ß2-agonis Helpful video	*Bronchodilators: • antimuscarinics : -unlike in asthma- antimuscarinic are superior to β2 agonists. • β2 agonists. *Inhaled glucocorticoids *Oxygen therapy *Antibiotics *Lung transplantation Helpful video

Summary of drugs used to treat asthma

taken from the doctor's lecture

Bronchodilators (relievers)

Drugs	Characteristics	Target
β2 agonists -Salbutamol ,terbutaline ———————— -Salmeterol , formoterol	• Short acting • Main choices of acute asthma • Inhalation ———————— • Long acting, Prophylaxis Nocturnal asthma	↑ Adenyl cyclase and cAMP
Antimuscarinics -Ipratropium (short acting) -Tiotropium (long acting)	• Main drugs for COPD • Inhalation	Block muscarinic receptors
Xanthine derivatives -Theophylline -Aminophylline	• orally or parenterally	Inhibit phosphodiesterase ↑ cAMP

Anti-inflammatory drugs (prophylactic)

	Drugs	Mode of administration
Corticosteroids inhibit phospholipase A2	Dexamethasone, Fluticasone, budesonide	**Inhalation**
	prednisolone	**Orally**
	Hydrocortisone	**parenterally**
Mast cell stabilizer	Cromoglycate (Cromolyn), Nedocromil	**Inhalation, prophylaxis in Children**
Cysteinyl LT1 Receptor antagonist	Zafirlukast, montelukast	**Orally**
Anti IgE antibody	Omalizumab	**Injection (SC)**

QUIZ

MCQs:

1-One of these acts Selectively on Beta 2 receptors with long acting period?
A-Isoprenaline. B-Epinephrine.
C-Albuterol. D-Salmeterol

2-The best drug to be given for status asthmaticus cases is:
A-Mast cell stabilizer. B-Leukotrienes antagonist.
C-Sympathomimetics. D-Glucocorticoids.

3-A 30-years old patient came to the ER with severe Asthma, he was given Glucocorticoids but with no response, which drug may work effectively in this case ?
A-Prednisone. B-Anti IgE Antibody.
C-Ipratropium. D-Nedocromil.

4-One of the ADRs of Pranlukast is :

A-Elevation of liver Enzymes. B-Burning sensation.
C-Bitter taste. D-Tremors.

5-In COPD which part of LRT is damaged:
A-Alveoli. B-Air sacs
C-Alveolar ducts. D-Respiratory bronchioles.

Answers
D, D, B, A, B

SAQ:

1-What is the mechanism of action of Mast cell stabilizers?

2-**Enumerate** THREE drugs belong to glucocorticoids

3-List FOUR side effects of glucocorticoids

4-Name one condition in which Aminophylline is indicated

Answers:

2-**act by stabilization of mast cell membrane.**They are **not** bronchodilators , so they are **not** effective in acute attack of asthma .
3-Budesonide & Fluticasone,beclometasone.
4-Adrenal suppression,Cataract,Psychosis, and Osteoporosis.
5-Status Asthmaticus.

pharmacology

Team 438

GOOD LUCK

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