

Drugs for asthma & 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.

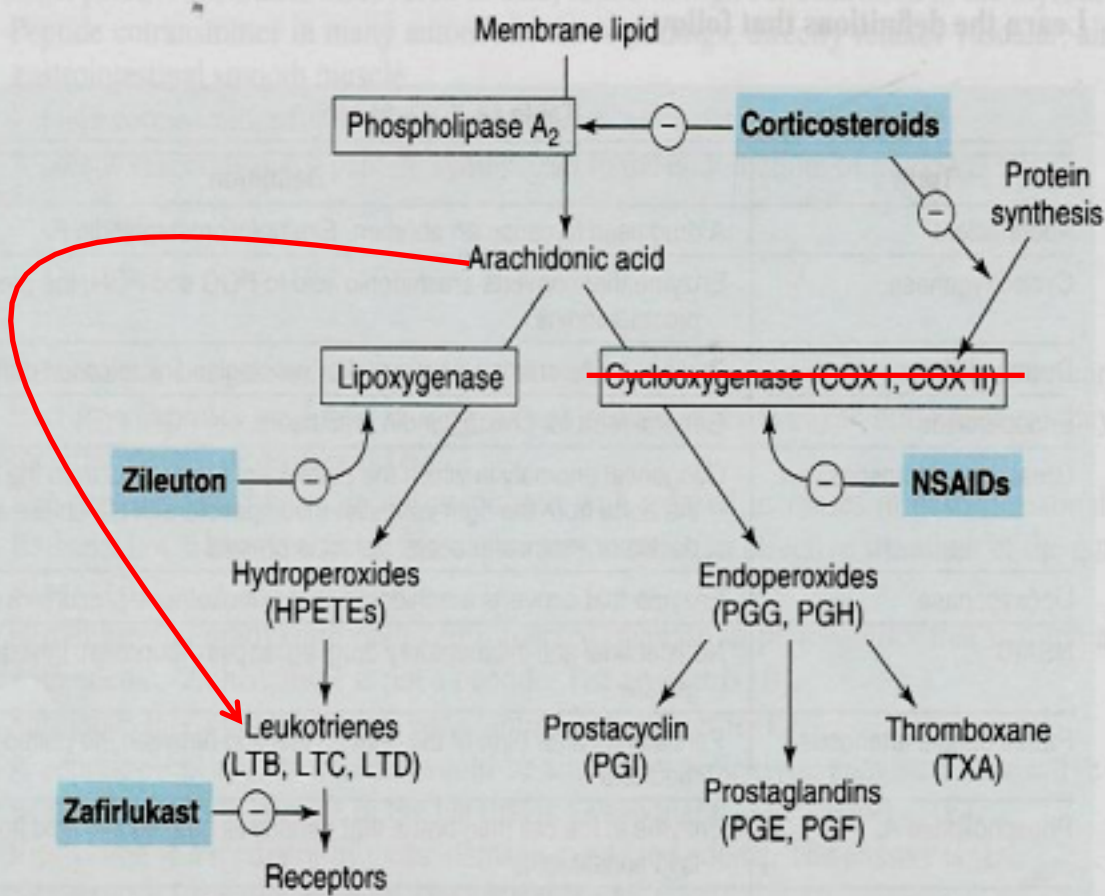


Don't be mean. Be above average.

- Titles
- Very important
- Extra information
- Doctor's notes

Bronchial asthma

<p>Definition</p>	<p>Asthma is a <u>chronic inflammatory disorder</u> 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).</p>
<p>Characters of airways in asthmatic patients</p> <p>1 ↓ Lead to 2 ↓ Lead to 3</p>	<p>1- Airway hyper-reactivity (sensitivity): abnormal sensitivity of the airways to any external stimuli which results into release of endogenous <u>inflammatory mediators</u> like histamine, leukotrienes . By antigen-antibody reaction (IgE)</p> <p>2- Inflammation (caused by hyper-reactivity)</p> <ul style="list-style-type: none">▪ ↑ edema, swelling▪ ↑ Thick mucus production. <p>3- Bronchospasm (constriction of the bronchial smooth muscles).</p>
<p>Symptoms of asthma</p>	<p>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.</p>
<p>Triggers</p>	<p>Chest Infection Stress Exercise (cold air) Pets Seasonal changes Emotional conditions Some drugs as aspirin, β-bockers Exogenous chemicals or irritants (perfume)</p>



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 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 B₂ 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	Prophylactic therapy
Bronchodilators (Quick relief medications)	Anti-inflammatory Agents (As Control medications)
treat acute attack of asthma <u>(These drugs can produce rapid relief of bronchoconstriction.)</u>	reduce the frequency of attacks
<ul style="list-style-type: none">❖ Short acting β₂-agonists❖ Antimuscarinics❖ Xanthine preparations	<ul style="list-style-type: none">❖ Corticosteroids❖ Mast cell stabilizers❖ Leukotrienes antagonists❖ Anti-IgE monoclonal antibody❖ Long acting β₂-agonists

Control the number of attacks

Quick relief medications

Bronchodilators (Quick relief medications)

treat acute attack of asthma

(These drugs can produce rapid relief of bronchoconstriction.)

❖ Short acting β_2 - adrenoreceptor agonists (\uparrow sympathetic output) 1st

choice of drugs

❖ Antimuscarinics (\downarrow parasympathetic output) 2nd choice

❖ Xanthine preparations 3rd choice

β - adrenoreceptor agonists (Sympathomimetics)

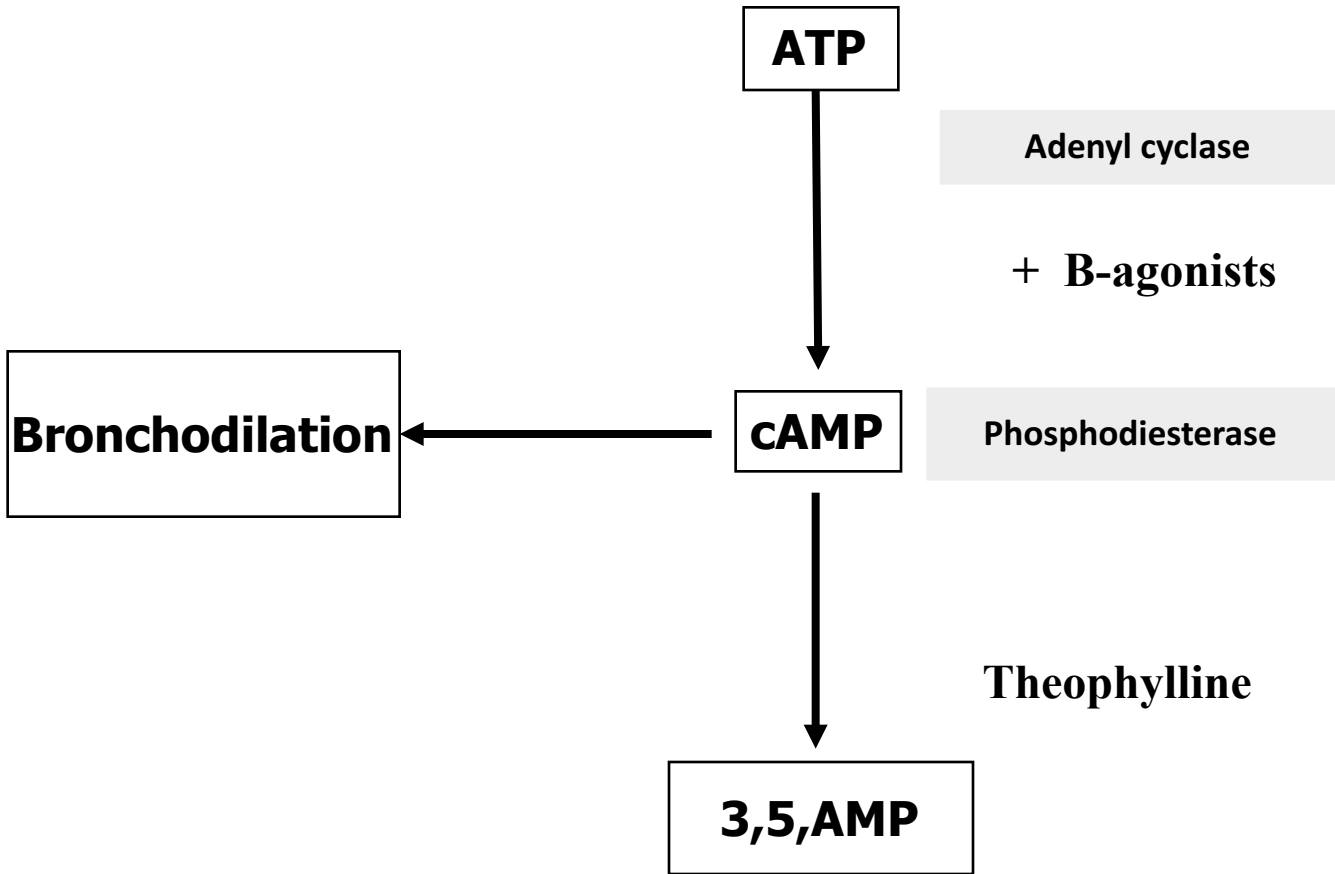
Non selective β agonists:	Selective β_2 – agonists (Preferable).
Epinephrine Isoprenaline doesn't work on a receptors Isoprenaline	Salbutamol (albuterol) Terbutaline Salmeterol Formeterol

Mechanism of Action:-

direct β_2 stimulation \rightarrow stimulate adenylyl cyclase $\rightarrow \uparrow$ cAMP \rightarrow bronchodilation.

Increase mucus clearance by (increasing ciliary activity).

Stabilization of mast cell membrane.



Non selective β agonists:

epinephrine

Administration

Given subcutaneously, S.C. , I.M.

Durations

rapid action (maximum effect within 15 min).

Has short duration of action (60-90 min).

Features

Drug of choice for acute anaphylaxis (*hypersensitivity reactions*).

Non-selective adrenergic agonist (α_1 , α_2 , β_1 , β_2).

Potent bronchodilator.

Disadvantages

❖ Not effective orally.

❖ Hyperglycemia

❖ Skeletal muscle tremor رعشة

❖ CVS side effects:

❖ tachycardia, arrhythmia, hypertension

❖ Not suitable for asthmatic patients with hypertension or heart failure.

Contraindications

CVS patients, diabetic patients

Selective β_2 –agonists (Preferable) has less side effect than non-selective β agonists
 Are mainly given by **inhalation** by (metered dose inhaler or nebulizer).



Can be given orally, parenterally.

Short acting β_2 agonist:

Salbutamol (inhalation, orally, i.v)

Terbutaline (inhalation, orally, s.c.)

- ❖ **Have rapid onset of action (15-30 min).**
- ❖ **short duration of action (4-6 hr)**
- ❖ **used for acute attack of asthma (drugs of choice).**

Advantages of β_2 agonists

- ❖ Minimal CVS side effects
- ❖ suitable for asthmatic patients **with CV** disorders as hypertension or heart failure.

أولادي عليان و أمول ما يجيبون لي الضغط والقلب عشان كذا احبهم

يمكن ترسل عليان و أمول للبيت بسرعة

- ترسل (TerSal)
- عليان و أمول (aline & Amol)
- للبيت (but)
- بسرعة (Short acting β_2 agonist)

Long acting selective β_2 agonists

Salmeterol & formoterol
 (are given by inhalation)

- ❖ Long acting bronchodilators (12 hours) due to high lipid solubility (creates depot effect).
- ❖ **are not used to relieve** acute episodes of asthma
- ❖ used for **nocturnal** asthma.(night asthma)
- ❖ combined with inhaled corticosteroids to control asthma (decreases the number and severity of asthma attacks).

Disadvantages of β_2 agonists

- ❖ Skeletal muscle tremors.
- ❖ Nervousness
- ❖ Tolerance (β -receptors down regulation).
- ❖ Overdose may produce tachycardia due to β_1 stimulation.

Is the LONG METRO FOR SALE?

الميترو الطويل هذا للبيع ؟

- الميترو (metro)
- الطويل (Long acting selective β_2 agonists)
- للبيع (For Sale)

2- Muscarinic antagonists:

(Second choice)

Tiotropium

Ipratropium

- 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)

has longer duration of action (24 hr).

has short duration of action (3-5hr).

Pharmacodynamics

- Inhibit bronchoconstriction and mucus secretion.
- Less effective than β 2-agonists.

Uses

- **Main choice in chronic obstructive pulmonary diseases (COPD).**
- In asthma combined with β 2 agonists and corticosteroids. (They both are bronchodilators with different mechanism of action, but in patients with (COPD) β 2 agonists can't relief the bronchoconstriction ,So we make this combination).
- **Never use as a rescue medication.** (Because β 2-agonists have more efficacy and rapid onset of action)

3-Methylxanthines: (3rd choice)

Aminophylline (For **status asthmatics** and is given as **slow infusion**)

أمانى وضعها صعب

Theophylline (Second line drug in asthma and is given **orally**)

TheO = The oral administration

Mechanism of action:

1-Phosphodiesterase inhibitors \uparrow cAMP \rightarrow 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)

2- Adenosine receptors antagonists (A1)

3-Increase diaphragmatic contraction

4-Stabilization of mast cell membrane

Similar effect of caffeine

Pharmacological effects:

- Bronchial muscle relaxation
- \uparrow contraction of diaphragm \rightarrow improve ventilation
- **CVS:** \uparrow heart rate, \uparrow force of contraction
- **GIT:** \uparrow gastric acid secretions
- **Kidney:** \uparrow renal blood flow, weak diuretic action
- **CNS stimulation:**
 - * stimulant effect on respiratory center.
 - * decrease fatigue & elevate mood.

Side Effects

Low therapeutic index (narrow safety margin) monitoring of theophylline blood level is necessary.

CVS effects: hypotension, arrhythmia.

GIT effects: nausea & vomiting

CNS side effects: * Overdose:
(tremors, nervousness, insomnia, convulsion)

Pharmacokinetics :

Metabolized by Cyt P450 enzymes in liver (All drugs metabolized by Cyt P450 must have drug drug interactions)

T $\frac{1}{2}$ = 8 hours

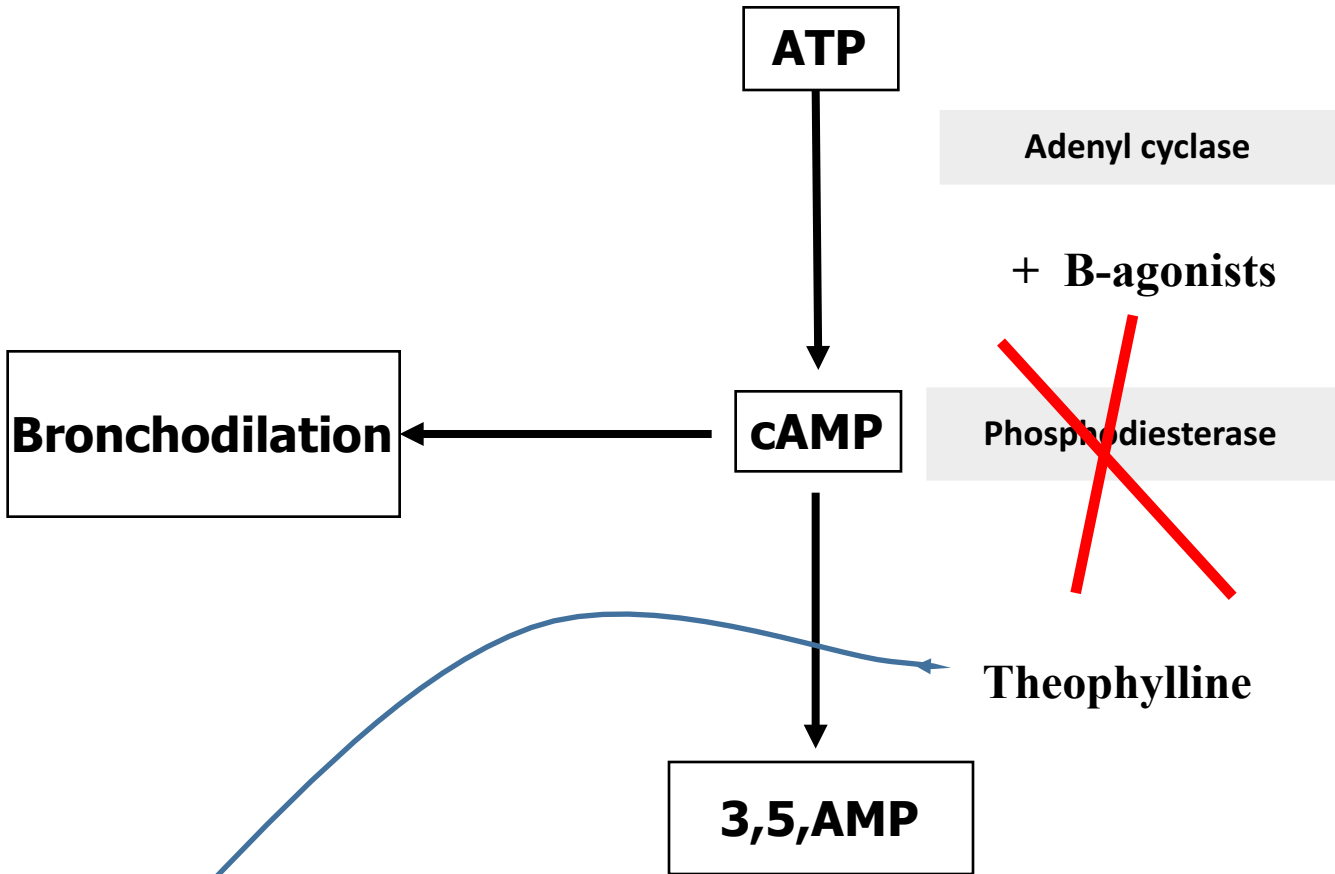
Drug interactions:

Enzyme inducers:

As phenobarbitone & rifampicin \rightarrow \uparrow metabolism of theophylline \rightarrow \downarrow T $\frac{1}{2}$.

Enzyme inhibitors:

as erythromycin \rightarrow \downarrow metabolism of theophylline \rightarrow \uparrow T $\frac{1}{2}$.



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)

Prophylactic Therapy

Prophylactic therapy:

(Control Medication) control the number of asthmatic attacks

Anti-inflammatory drugs include:

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

(control medications /prophylactic therapy)

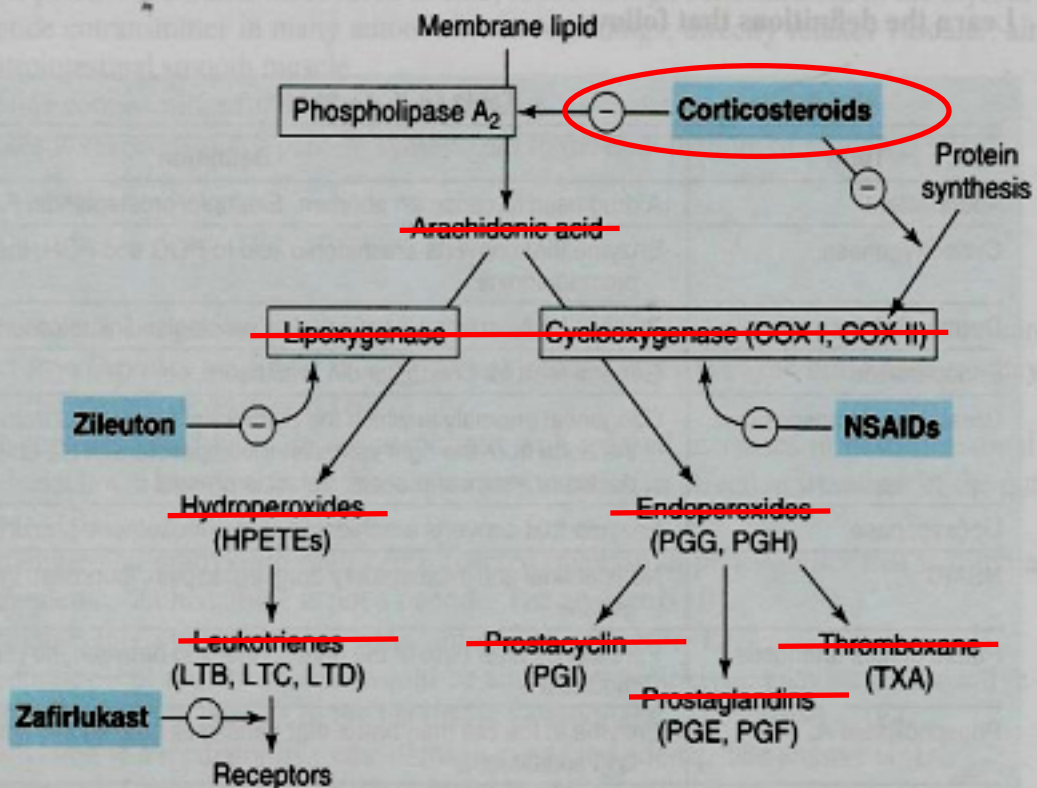
1- ↓ bronchial hyperreactivity.

2- ↓ reduce inflammation of airways

1 → 2 → 3

3- ↓ reduce the spasm of airways

1-



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 $\beta 2$ receptors** (have additive effect to $\beta 2$ 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.

We can avoid its side effect by avoiding systemic administration
And give them (orally , injection)

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:

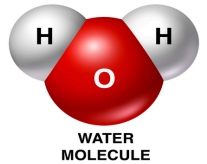
(Hydrocortisone, dexamethasone)

Sone or methasone = Corticosteroids

باللبناني تصير ..
بدي فلوت بيكلو .. لان ريحته بنتشهي



Orally = lips
• بردن شفتاك (Predn)
• أو شفتاك حمراء (red lips)



Injection = Water like
Dihydrogen monoxide

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 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.



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).

Washing mouth after inhalation will decrease the side effect

- Dysphonia (voice hoarseness).

Withdrawal of systemic corticosteroids :

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

Mast cell stabilizers

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

حليب نيدو (Nedo) والجلي (Gly) والكريم كراميل (Cromo cromil) كلها كانت بدرجة تشبه حبيبات (Histamine) وبعد ما نضيف المويه ونحطها بالثلاجة تبدأ تتماسك وتثبت (Mast cell stabilizers)

Mechanism of action:

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

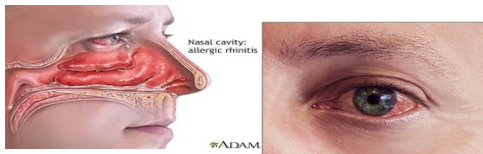
Pharmacodynamics:

- 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:

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

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



Side effects :

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

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.

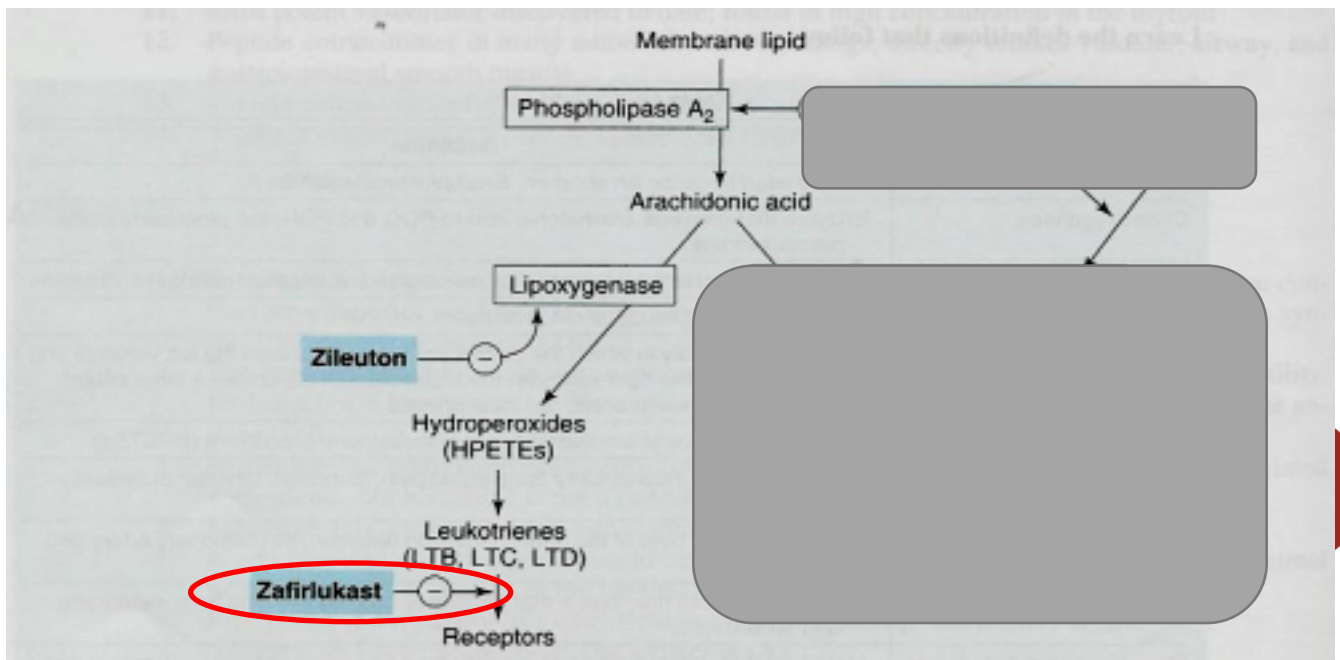
Leukotriene B4: chemotaxis of neutrophils

كانها تمشي قدام النيوتروفيل عشان تدلها وين مكان
الانفلاميشن وتقول انا قبلك Before (B4) you

Cysteinyl leukotrienes C4, D4 & E4.

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

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



Mechanism of action of leukotrienes antagonists :

e.g.

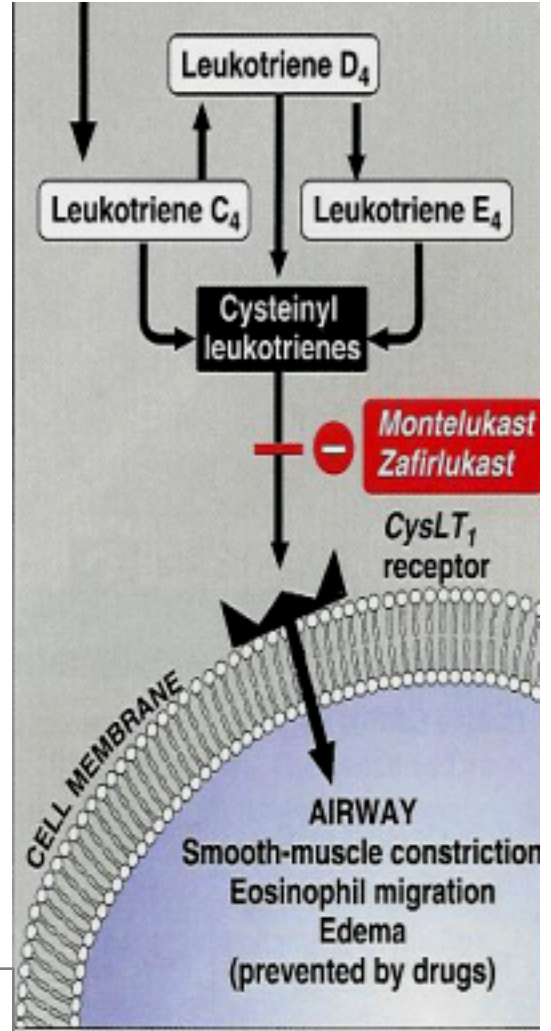
Zafirlukast

Montelukast

Pranlukast

are selective, reversible antagonists (blocking) of cysteinyl leukotriene receptors (**CysLT₁ receptors**)*.

* Cysteinyl leukotrienes



CysLT₁receptors وظيفة هذه الأدوية انها تسوي بلوك ل

Luk = Leukotriene = lock or block the receptor

ظافر سوا مقلب بمدينة مونت كارلو (Zafir did a prank in monte carlo)

ظافر (Zafir) أكل مندي (Monte) برا (Pra)





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.
 - e.g. aspirin-induced asthma
 - e.g. antigen and exercise-induced asthma.
- Can be combined with glucocorticoids (additive effects, low dose of glucocorticoids can be used).

Side effects:

Elevation of liver enzymes, headache, dyspepsia



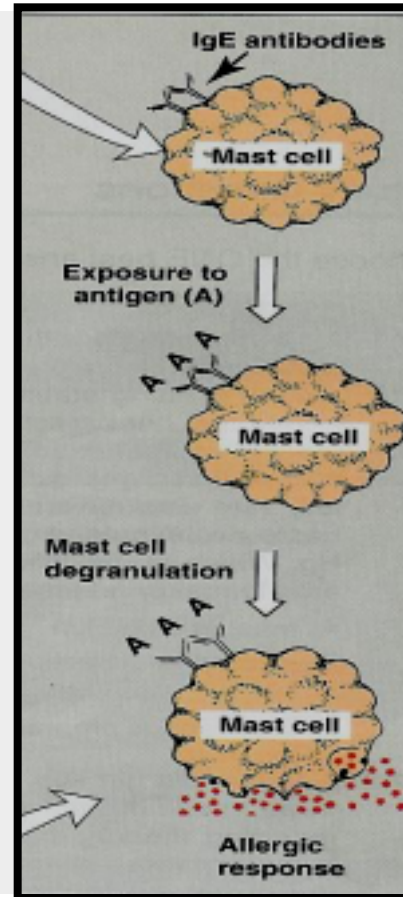
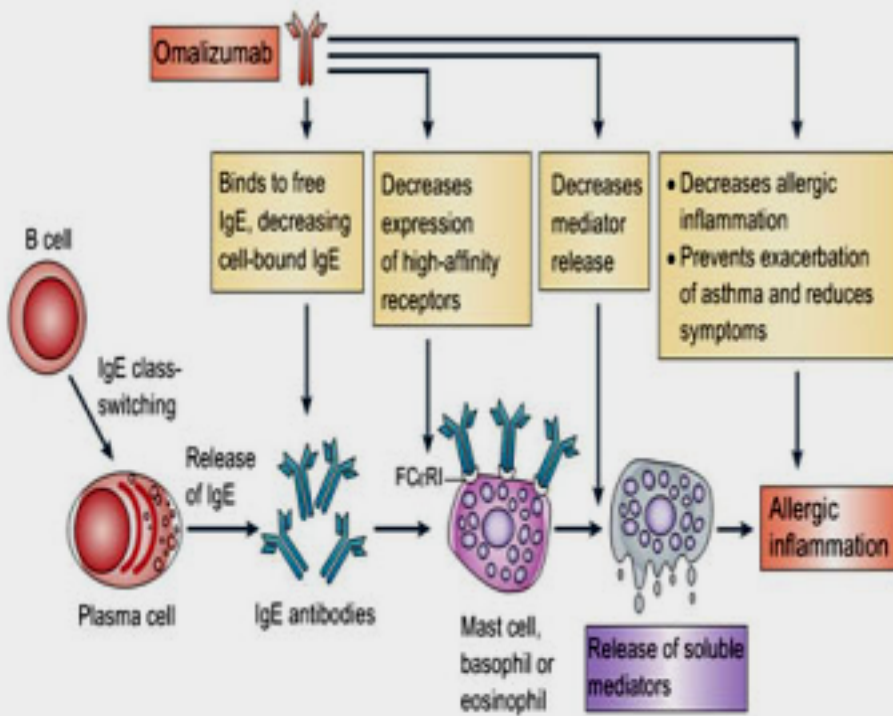
Anti-IgE monoclonal antibody

e.g. **Omalizumab**

أي (IgE) أعرف أم علي (Om Ali) من عائلة (Zumab)

- 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



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

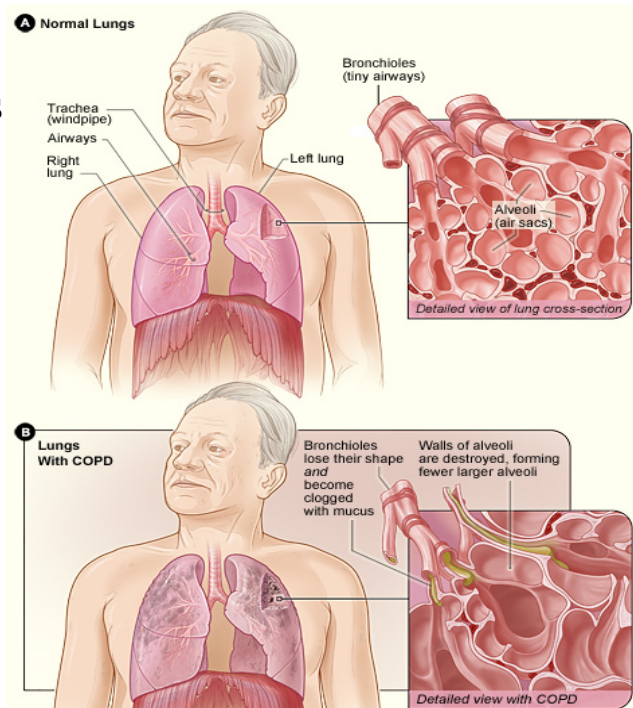
COPD

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.

Treatment:

- **Antibiotics** specifically macrolides such as of exacerbations.
- Inhaled bronchodilators .
- Inhaled glucocorticoids .
- Oxygen therapy .
- Lung transplantation .



Inhaled bronchodilators in COPD :

- Inhaled antimuscarinics

- Ipratropium & tiotropium .
- are superior to β_2 agonists in COPD .

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

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

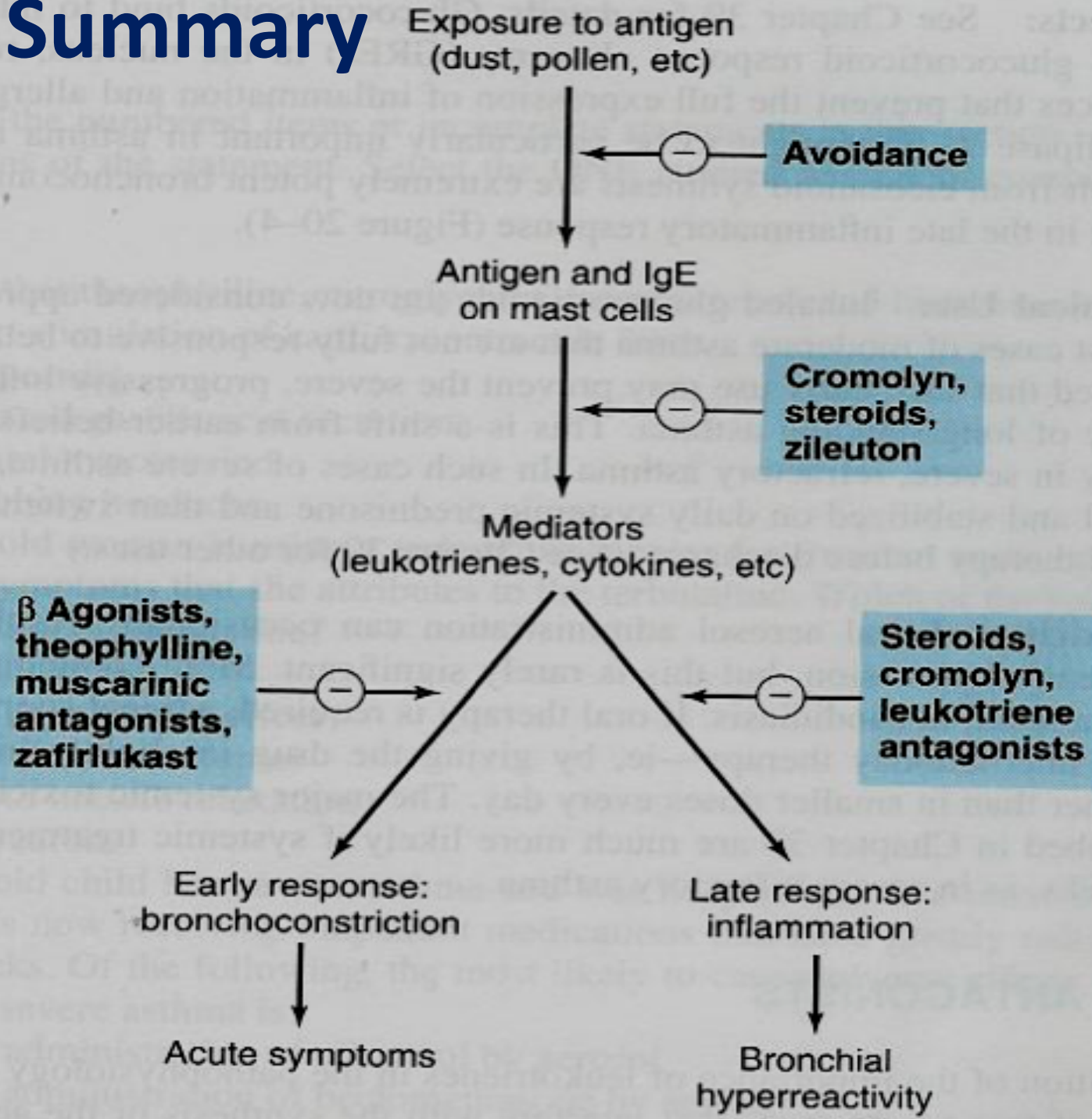
Bronchodilators (relievers for bronchospasm)

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 receptors
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

Summary



A 12-year-old girl with a childhood history of asthma complained from a cough, dyspnea, and wheezing after visiting a riding stable. Her symptoms became more worse so her parents brought her to the emergency room.

Q1: what is the drug of choice in this case to rapidly reverse her bronchoconstriction?

Short acting β_2 -agonists such as (Salbutamol or Terbutaline).

Q2: What is the mechanism of action ?

Act as β_2 -agonist which lead to stimulate the β_2 receptors \rightarrow stimulate adenylyl cyclase \rightarrow increase cAMP \rightarrow bronchodilation.

Q3: What is the best route of administration for this drug and why ?

Inhalation, to minimize the side effects and be localize.

Q4: Why we can not use the Adrenaline in this case even though it is considered as a potent bronchodilator ?

Because it is non-selective adrenergic agonist which act on [α_1 , α_2 , β_1 , β_2 , β_3], so it has many side effects. It even can reserve it for acute anaphylaxis .

Q5: List some contraindication for Adrenaline drug ?

CVS patients such as hypertension or heart failure / diabetic patients.

Q6: If the drug that you mention in the 1st question does not work or its not available in the pharmacy or even the case is so sever, what other options do we have as a 2nd drug of choice?

Xanthine preparations (Methylxanthines) Such as aminophylline is good choice for status asthmatics.

Q7: Later, we know that she could not sleep well because the asthma attack gets worse at night . Is there any bronchodilator drug is recommended ?

Long acting bronchodilators selective β_2 agonists such as (Salmeterol & formoterol) can help in nocturnal asthma. Because they have depot effect due to high lipid solubility so its $t_{1/2}$ is about 12 hours.

A 9-year-old girl has asthma, she was given salbutamol as bronchodilator. She used the inhalation three times per week but did not help her. Two weeks later, her asthma gets worse and she could not sleep at night due severe attack which required three hospitalizations in the last year. She is now receiving therapy that has greatly reduced the frequency of these severe attacks. Which is a combination of β_2 agonists and Glucocorticoids.

Q1: why this combination was responsible for this benefit?

Because the Glucocorticoids have additive effect to β_2 agonists by acting as upregulate β_2 receptors.

Q2: What is the main mechanism of action of Glucocorticoids ?

Inhibition of phospholipase A2 \rightarrow Decrease prostaglandin and leukotrienes \rightarrow Decrease Number of inflammatory cells in airways.

Q3: Glucocorticoids can be administrated in many routes. The Inhalation is the Best choice in asthma because it has less side effects. List some of them ?

1\ Oropharyngeal candidiasis (thrush). 2\ Dysphonia (voice hoarseness).

Q4: Glucocorticoids can be administrated in many routes. List some of them and support them with two drug as an example .

•Orally \rightarrow Prednisone, methyl prednisolone
•Injection \rightarrow Hydrocortisone, dexamethasone

Q5: List some clinical uses of Glucocorticoids other than in asthma ?

1\ Treatment of inflammatory disorders such as rheumatoid arthritis 2\ After transplantation as immunosuppressants.
3\ Treatment of autoimmune disorders such as ulcerative, colitis, psoriasis. 4\ Antiemetics in cancer chemotherapy

Q6: Why should we avoid abrupt or sudden stop of corticosteroids especially if they are given systemically and the dose should be reduced gradually ?

To avoid adrenal insufficiency syndrome.

Q7: Which group of drugs can be used with glucocorticoids as a combination to minimize its side effects by decreasing the dose of glucocorticoids ? (other than β_2 agonists)

leukotrienes antagonists have additive effects When they are combined with glucocorticoids (sparing effect).

QUIZ



Boys	Girls
عبدالرحمن ذكري	غادة المهنا
عبدالعزيز رضوان	اللولو الصليهم
مؤيد أحمد	روان القحطاني
فيصل العباد	امل القرني
فارس النفيسة	شروق الصومالي
خالد العيسى	سما الحربي
عبدالرحمن العريفي	انوار العجمي
عبدالرحمن الجريان	وتين الحمود
محمد خوجة	رنا باراسين
عمر التركستاني	

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