

Pharmacology of drug used in the bronchial asthma

EDITING FILE

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Objectives:

IT IS HIGHLY RECOMMENDED TO STUDY **PATHOLOGY & IMMUNOLOGY** LECTURES, AND **ADRENERGIC AGONISTS & ANTICHOLINERGIC DRUGS** LECTURES. BEFORE THIS TO HAVE A **BETTER UNDERSTANDING** OF THE CONCEPTS.



List 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.



In general focus on:
1- Major side effect.
2- drug of choice for each condition.
3- M.O.A



Bronchial Asthma

Asthma is a **chronic inflammatory disorders** of bronchial airways that result in airway obstruction in response to external stimuli (as pollen grains, cold air and tobacco smoke).



- Infection (if untreated).
- Stress (cause **AvTIVATION** of **SYMPATHETIC** system).
- Exercise (cold air) (cause **relase of histamine**).
- Pets حيوانات أليفة
- Seasonal changes.
- Emotional conditions.
- Some drugs as aspiRIN & β -bockers.
- Genetic factors.



Symptoms:

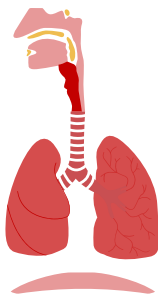
- **Asthma produces recurrent episodic attack of:**
 - Acute bronchoconstriction
 - Shortness of breath.
 - Chest tightness.
 - Wheezing.
 - Rapid respiration.
 - Cough.
- **Symptoms can happen each time the airways are irritated by inhaled irritants or allergens.**

INNERVATION OF RESPIRATORY SYSTEM

Parasympathetic supply

M3 receptors in smooth muscles and glands.

- Bronchoconstriction
- Increase mucus secretion.



No sympathetic supply

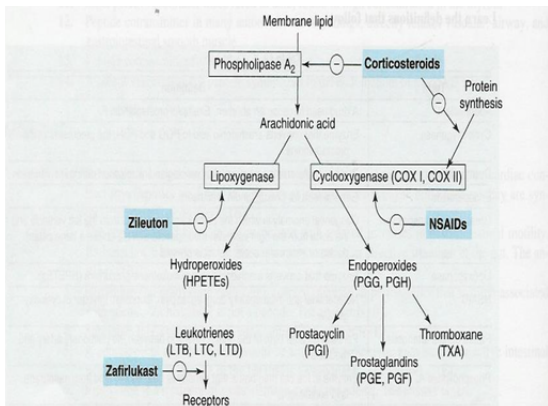
(there's only receptors)

- β_2 receptors are located on smooth muscle and glands.
- Bronchodilation
 - Decrease mucus secretion.

The parasympathetic nervous system is the dominant neuronal pathway in the control of airway smooth muscle tone.

Bronchial Asthma cont

EXTRA INFO



Explanation:

Corticosteroids inhibit phospholipase A₂ production by boosting production of lipocortin, an inhibitor protein. While The main mechanism of action of NSAIDs and paracetamol is the inhibition of the enzyme cyclooxygenase (COX) which is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins.

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.

Anti-asthmatic Drugs

Quick Relief medications (Treatment)

Bronchodilators used to treat acute episodic attacks of asthma.
These drugs can produce rapid relief of bronchoconstriction.

1- Short acting β 2-agonists.
(β 2 adrenoceptor agonist -best choice-)

2- Antimuscarinic.
(Atropine derivative)

3- Xanthine preparations.

Control medications (prophylactic therapy)

Glucocorticoides; Anti-inflammatory drugs used to reduce the frequency of attacks, and Nocturnal Awakenings.
الاستيقاظ الليلي

- 1- Corticosteroids.
(The most potent anti inflammatory drugs).
- 2- Mast cell stabilizers
(To stop the release of histamine).
- 3- Leukotrienes antagonists.
- 4- Anti-IgE monoclonal antibody.
- 5- Long acting β 2-agonist.



Sympathomimetics - adrenoceptor agonists



Important

CLASSIFICATION OF β AGONISTS

Selective β_2 - agonists

(Preferable):

Short acting:

- Salbutamol (albuterol)

- Terbutaline

Long acting:

- Salmeterol

- Formoterol

Non selective β agonists:

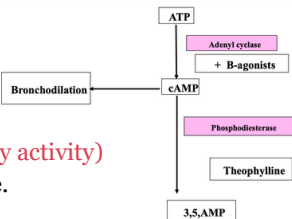
Epinephrine

(Adrenaline) &

Isoprenaline.

MECHANISM OF ACTION:

- increase mucus clearance by (increasing ciliary activity)
- Stabilization of mast cell membrane.



DIRECT β_2
STIMULATION



STIMULATE
ADENYL CYCLASE



↑ cAMP



BRONCHODILATION





Non selective B-Agonist


Drugs	Epinephrine (Adrenaline)	Isoprenaline
clinical uses	<ul style="list-style-type: none">• Potent Bronchodilator.• Adrenaline is the drug of choice for acute anaphylaxis(hypersensitivity reaction).	
Pharmacokinetics	<p>Adrenaline Non-selective adrenergic agonist (α_1, α_2, β_1, β_2).</p> <p>Isoprenaline: non-selective Beta agonist</p> <ul style="list-style-type: none">• Given subcutaneously, S.C ,IM.• Not effective orally (disadvantage).• Rapid onset of action (maximum effect within 15 min).• Has a short duration of action (60-90 mins).	
ADRs	<ul style="list-style-type: none">• Hyperglycemia.• Skeletal muscle tremor (due to β_2 effect, could happen but rare).• CVS side effects:<ul style="list-style-type: none">- Tachycardia- Arrhythmia- Hypertension	
Contraindications	<ul style="list-style-type: none">• CVS patient.• Diabetic patients.• Asthmatic patients with hypertension or heart failure.	

Selective B2 Agonist (Preferable)

Mainly given by inhalation by: metered dose inhaler or nebulizer

	Short acting β 2 Agonist	Long acting β 2 Agonist
Drugs	<p>1- SALBUTAMOL (ALBUTEROL): Inhalation, orally, i.v. (أهم واحد من بينهم ويتم استخدامه بكثرة لمرضى الربو)</p> <p>2- TERBUTALINE: Given by inhalation, orally, S.C.</p>	<p>1- SALMETEROL 2- FORMOTEROL</p> <p>Both are given by inhalation <small>(صلاة الأربع ركعات أطول مدة long duration من الركعتين) "FOR" ← أربع "SAL" ← صعل</small></p>
clinical uses	<p>Drugs of choice for acute episodic attack of asthma</p>	<p>Not used to relieve acute attacks of Asthma.</p> <ul style="list-style-type: none">- Used for nocturnal Asthma- Combined with inhaled corticosteroids to decrease the number and severity of Asthma attacks, such as (formoterol + Budesonide). (Control asthma).
Pharmacokinetics	<p>Have a rapid onset action (15-30 min). Short duration of action (4-6 hr).</p>	<p>Long acting Bronchodilators (12 hr) due to high lipid solubility (creates depot effect).</p>
Advantages	<p>1- Minimal CVS side effects. 2- Suitable for Asthmatic patients with CV disorders as hypertension or heart failure.</p>	

Disadvantages










1- **Skeletal muscle tremors** (A common characteristic. Activation of adrenergic receptors on skeletal muscles → hypokalemia → tremors)

2- **Nervousness.**

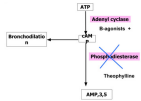
3- **Tolerance** (β -receptor down regulation). (if this happen we will combine it with corticosteroid) Normally receptors are internalized **Important** into the cell to be recycled, repeated use can decrease the number of receptors beyond recycling making the cells less sensitive to a hormone or another agent.

4- Overdose may produce **tachycardia** due to β_1 stimulation. (losing selectivity).

Muscarinic Antagonist (Second Choice)

Drugs	^{atropine} إبرة Ipratropium	Tiotropium خيط طويل
 Duration	Short duration of action (3-5) h الإبرة قصيرة	Longer duration of action (24) h الخيط طويل
 M.O.A 	Act by blocking muscarinic receptor, (non-selective)	
Pharmacodynamics	-Inhibit bronchoconstriction and mucus secretion. (Not direct bronchodilation effect). -Less effective than B2-Agonist.	
 USES 	- Main choice in COPD. - In acute severe asthma combines with B2- Agonists & Corticosteroids. - Never use as rescue medication.	
 Pharmacokinetics	<ul style="list-style-type: none">• Given by Aerosol inhalation.• Have a delayed onset of action.	
 Other Characteristics	<ul style="list-style-type: none">• Quaternary derivatives of Atropine (polar).• Does not diffuse into the blood.• Does not enter CNS.• Have minimal systemic side effect.	

Methylxanthines (Xanthine preparations)

Drugs	Theophylline	Aminophylline
<p>★ ★</p> <p>M.O.A</p>	<p>1- Phosphodiesterase inhibitors: \uparrow cAMP \rightarrow bronchodilation. 2- Adenosine receptors antagonists (A1). 3- Increase diaphragmatic contraction. 4- Stabilization of mast cell membrane.</p> 	
<p>★ ★</p> <p>Pharmacological effects</p> <p>مثل تأثير شرب القهوة.</p>	<ul style="list-style-type: none"> • Bronchial muscle relaxation. • \uparrow Contraction of diaphragm \rightarrow improve ventilation. • CVS: \uparrow Heart rate, \uparrow Force of contraction. • GIT: \uparrow Gastric acid secretions (contraindicated in patients with peptic ulcers) • Kidney: \uparrow Renal blood flow, weak diuretic action. • CNS stimulation: <ol style="list-style-type: none"> 1. Stimulant effect on respiratory center. 2. Decrease fatigue & elevate mood. 3. Overdose: tremors, nervousness, insomnia, convulsion. 	
<p>Administration</p>	<p>Given orally</p>	<p>Given as slow infusion</p>
<p>Pharmacokinetics</p>	<p>T $\frac{1}{2}$ = 8 hours Metabolized by Cyt P450 enzymes in liver. ★</p> <p>has many drugs interactions:</p> <ol style="list-style-type: none"> 1. Enzyme inducers (phenobarbital & rifampicin): \uparrow metabolism of theophylline \rightarrow \downarrow T $\frac{1}{2}$. 2. Enzyme inhibitors (erythromycin + Cimetidine): \downarrow metabolism of theophylline \rightarrow \uparrow T $\frac{1}{2}$. 	
<p>★ Uses ★</p>	<p>Second line drug in asthma</p>	<p>For status asthmaticus</p>

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.



Prophylactic Therapy (Control Medication)

Anti-inflammatory drugs:

1

GLUCOCORTICOIDS

2

LEUKOTRIENES
ANTAGONIST

They are control medications / prophylactic therapy act by:

- ↓ Bronchial hyper-reactivity.
- ↓ Reduce inflammation of airways.
- ↓ Reduce the spasm of airways.

3

MAST CELL
STABILIZERS

4

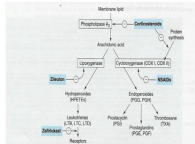
ANTI-IGE
MONOCLONAL
ANTIBODY
E.G. OMALIZUMAB

Glucocorticoids

M.O.A

Anti-inflammatory action due to:

- inhibition of phospholipase A2.
- ↓ Prostaglandin and leukotriene .
- ↓ 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 B2 agonists). (means that glucocorticoids increase the effect of B2 agonist.)



Important

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.

Administration



Inhalation:

- Given by inhalation (metered-dose inhaler).
- Have first pass metabolism
- Best choice in asthma, less side effects.

e.g. **Budesonide, Fluticasone and beclometasone.**

- **Orally: Prednisone, methyl prednisolone.** (For acute asthma attack).
- **Injection: Hydrocortisone, dexamethasone.** (used in status asthmaticus).



<p>Glucocorticoids in Asthma</p>	<ul style="list-style-type: none"> • 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 $\beta 2$ agonists.
<p>Clinical Uses</p>	<ul style="list-style-type: none"> • Treatment of inflammatory disorders (asthma, rheumatoid arthritis). • Treatment of autoimmune disorders (ulcerative colitis, psoriasis) and after organ or bone marrow transplantation as immunosuppressants. • Antiemetics in cancer chemotherapy.
<p> Side effects due to systemic corticosteroids</p>	<ol style="list-style-type: none"> 1. Adrenal suppression, (Cortisol produced by the adrenal gland). 2. Growth retardation in children. 3. Osteoporosis. 4. Susceptibility to infections. (immunosuppressant). 5. Fluid retention, weight gain, Hypertension. 6. Hyperglycemia. 7. Fat distribution. 8. Cataract (ماء ابيض على عدسات العين). 9. Psychosis.
<p> side effects due to Inhalation</p>	<p>Inhalation has very less side effects, but can cause:</p> <ul style="list-style-type: none"> • Oropharyngeal candidiasis (thrush). Fungal infection by Candida species caused by the suppression of normal flora and the pathogen. Important • Dysphonia (voice hoarseness) Rinse properly to reduce these effects.
<p>Withdrawal of systemic corticosteroids</p>	<p>Abrupt (sudden) stop of corticosteroids should be avoided and dose should be tapered (adrenal insufficiency syndrome). Administration and withdrawal should be gradual.</p>

Cont... Glucocorticoids

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

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

Very Important



1

using inhaled β_2 agonists **three times/week**

2

symptomatic **three times/week** or more

3

or waking **one night/week**. (بسبب الكتمة).

Mast Cell Stabilizers

Drugs	Cromoglycate (cromolyn)	Nedocromil نيدو كراميل
M.O.A	<ul style="list-style-type: none">• Act by stabilization of mast cell membrane.• Given by inhalation (aerosol, nebulizer).• Have poor oral absorption (10%).	
Uses	<ul style="list-style-type: none">• Prophylactic therapy in asthma especially in children.• Allergic rhinitis.• Conjunctivitis.	

Pharmacodynamics

- They are **not** bronchodilators, so they are **not** effective in acute attack of asthma.
- Prophylactic drug.
- Reduce bronchial hyperreactivity. "No histamine = No inflammation"
- Effective in exercise, antigen and irritant-induced asthma.
- Children respond better than adults.

Side effects

- Bitter taste.
- Minor upper respiratory tract irritation (burning sensation, nasal congestion).

Leukotrienes Antagonists

Drugs

Zafirlukast

Montelukast

Pranlukast

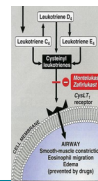
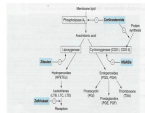
Target



- 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, ↑ bronchial hyperreactivity, ↑ mucosal edema and mucus secretion.

M.O.A & Pharmacodynamics

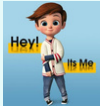

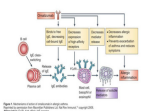

- **Selective, reversible antagonists of cysteinyl leukotriene receptors (CysLT1 receptors).**
- Bronchodilators.
- Have anti-inflammatory action.
- Less effective than inhaled corticosteroids.
- Have glucocorticoids sparing effect.

اسبيير



Administration	Taken orally.
 Uses	<ul style="list-style-type: none"> • 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).
 Side effects	<ul style="list-style-type: none"> • Elevation of liver enzymes (نتابع عمل الكبد أثناء العلاج). • Headache • Dyspepsia <p style="text-align: right;">Important</p>

Anti-IgE Monoclonal Antibody

Drug	 أم علي Omalizumab
 M.O.A & pharmacodynamics	<ul style="list-style-type: none"> • A monoclonal antibody directed against human IgE. given by injection (s.c.). • Prevents IgE binding with its receptors on mast cells & basophiles. • Decrease the release of allergic mediators. <div style="display: flex; justify-content: space-between; align-items: center;">  <div style="text-align: right;"> <p>Hint: Suffix “mab “means monoclonal antibody >> not given orally because it is protein and will be digested</p> </div> </div>
Disadvantages	Expensive-not first line therapy.
 Uses	Used for treatment of moderate to severe allergic asthma which does not respond to high doses of corticosteroids.

“ study smarter , not harder “

Active recall



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summary



MCQs

1

A 10 years old patient takes salbutamol as a treatment of asthma, he came to the emergency because the drug dose not work anymore. which of the following you will give him to increase the effect of the drug?

A Omalizumab

B Prednisone

C Terbutaline

D Zafirlukast

2

An asthmatic patient undergo Budesonide therapy, which of the following he will present as a side effect?

A Tremors

B Hyperkalemia

C Thrush

D Hypotension

3

Which drug would be appropriate to consider for an 8-year-old girl who presents with symptoms of dry mouth, cough, and wheezing, along with Monday night episodes of shortness of breath, while already using inhaled β_2 agonists three times a week?

A Omalizumab

B Salbutamol

C Salmeterol

D Fluticasone

4

A 12 years old boy had a headache, his friend gave him aspirin and with time he started to feel short of breathing and coughing, he went to the hospital and the doctor prescribe him a drug that relieved him. The doctor was worried about liver function if he continues in using the drug, what is the drug?

A Aminophylline

B Terbutaline

C Montelukast

D Formoterol

MCQs

5

A 9 years old girl takes certain drug, she had skeletal muscle tremors. what is the cause of her condition?

A Leukotrienes antagonist

B Mast cell stabilizers

C Glucocorticoids

D B2 agonists

6

A patient diagnosed with status asthmaticus, the doctor gave him a drug but the patient showed tremors, increase in heart rate, and weak diuretic action. what is the drug?

A Theophylline

B Salmeterol

C Aminophylline

D Adrenaline

7

An asthmatic patient was taking salbutamol, the doctor started giving him dexamethasone. after a while he suddenly returned to salbutamol without consulting the doctor. which of the following will he have?

A Nervousness

B Adrenal insufficiency syndrome

C Osteoporosis

D Cataract

8

Ali's mother has sever allergic asthma. The doctor give her high doses of Fluticasone but she dose not respond to it, he give her an expensive drug work against antibodies. what is the drug?

A Omalizumab

B Omomarzumab

C Ipratropium

D Nedocromil

SAQs

1 Mention 2 ways that used to manage Asthma.

◆ 1 - by Quick Relief medications.
2 - by Control medications.

2 list the types of drugs used in one way from the above.

◆ Short acting β_2 -agonists, Antimuscarinic, Xanthine preparations.
or
Corticosteroids, Mast cell stabilizers,
Leukotrienes antagonists, Anti-IgE monoclonal
antibody, Long acting β_2 -agonists.

3 Give two drugs of one type from above.

◆ Possible answer: Cromoglycate,
Nedocromil.

4 How the drug interactions will happen to theophylline?

◆ Enzyme inducers (phenobarbital & rifampicin): ↑ metabolism of theophylline → ↓ 7%.
◆ Enzyme inhibitors → ↑ 7%.
◆ (erythromycin+Clometidine): ↑ metabolism of theophylline → ↑ 7%.



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