Pharmacotherapy of Bronchial Asthma

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Objectives

- This subject will be covered in two lectures

❖The principal drugs used in asthma

❖Classification of these drugs according to mechanism of action

❖The quick-relief drugs of asthma

❖Drugs used in prophylaxis of asthma

What is bronchial asthma?

- Bronchial asthma is a chronic **inflammatory** airways disease, that is characterized by **hyper-responsiveness** of the airways to certain stimuli, and resulted in recurrent reversible attacks of **bronchoconstriction**

Pathophysiology

Allergic stimuli **Non-allergic stimuli**

IgE ← **Anti-IgE AB**

Inflammation*

hyper-responsiveness

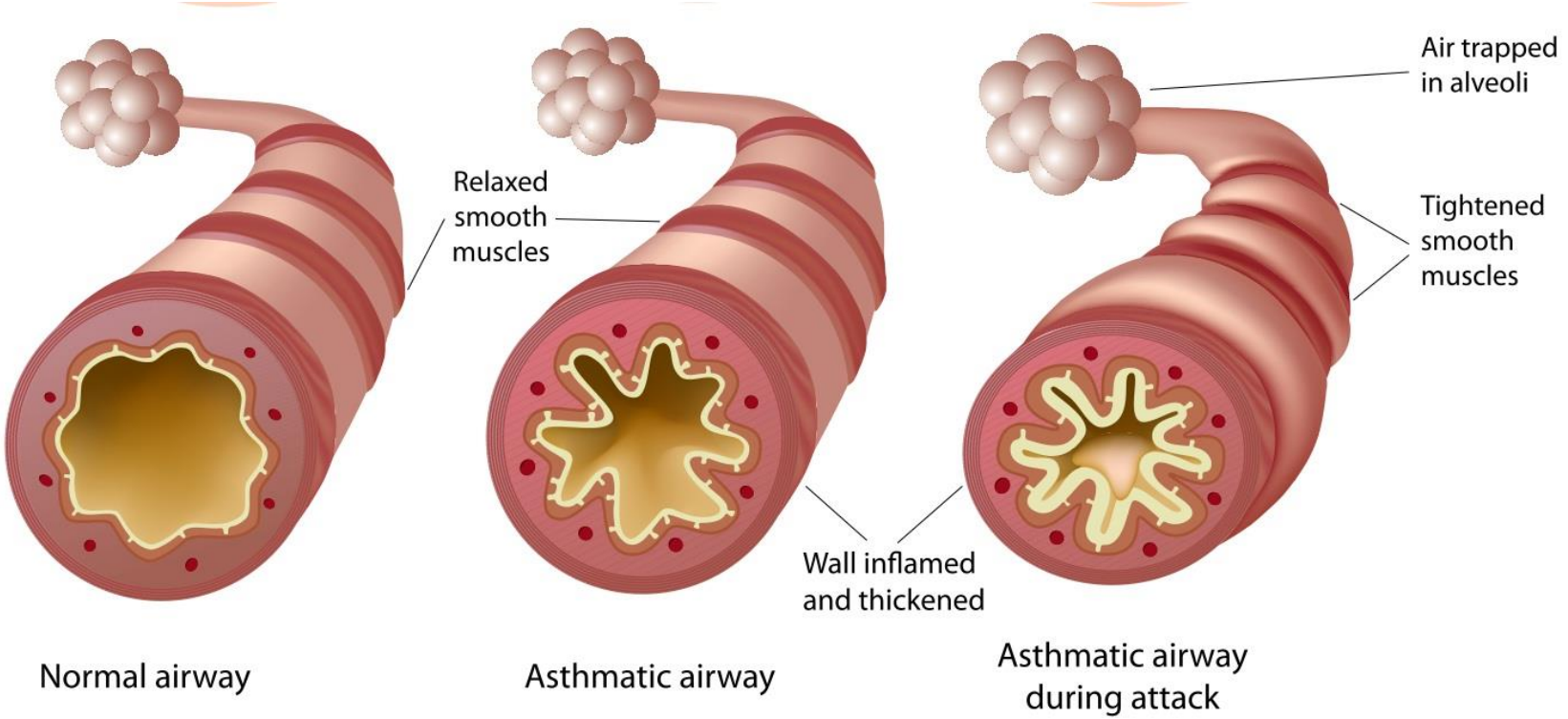
Anti inflammatory

Stabilizers

Bronchodilators

Bronchospasm

(Shortness of breath, wheeze…)


Relaxed
smooth
muscles
Air trapped
in alveoli
Tightened
smooth
muscles
Wall inflamed
and thickened
Normal airway
Asthmatic airway
Asthmatic airway
during attack

Classification according to mechanism of action

1. Drugs that decrease airways inflammation and hyper-responsiveness

(Anti-inflammatory drugs): **Corticosteroids**

Leukotrienes pathway modifiers

Mast cell stabilizers

2. Bronchodilators: **β_2 agonists**

Xanthine derivatives

Anticholinergics

Anti inflammatory drugs

Membrane phospholipids

Phospholipase A2

Corticosteroids

Leukotrienes modifiers

????

Arachidonic acid

Cyclo-oxygenase

5- lipo-oxygenase

PGs

Leukotrienes

(bronchoconstriction, mucosal edema, chemotaxis)

Glucocorticoids

Mechanism of action in asthma

1-Inhibit the inflammatory response to Ab-Ag reaction:

Inhibit influx of inflammatory cells

Inhibit synthesis of inflammatory mediators & chemokines

Inhibit release of inflammatory mediators

Decrease mucosal edema

2. Decrease bronchial mucous secretion

3. Increase number & sensitivity of endogenous β_2-receptors

Types of glucocorticoids

1. **<u>Inhalational steroids</u>**: use in chronic asthma

e.g. Fluticasone, Budesonide, Beclomethasone

- These drugs are highly lipid soluble with extensive 1st pass metabolism, so if systemic absorption occur, systemic side effects are less likely to occur
- Initial response noticed after 6-8 hr., with maximum response 1-2 weeks later

Metered dose inhaler

Dry powder inhaler

nebulizer

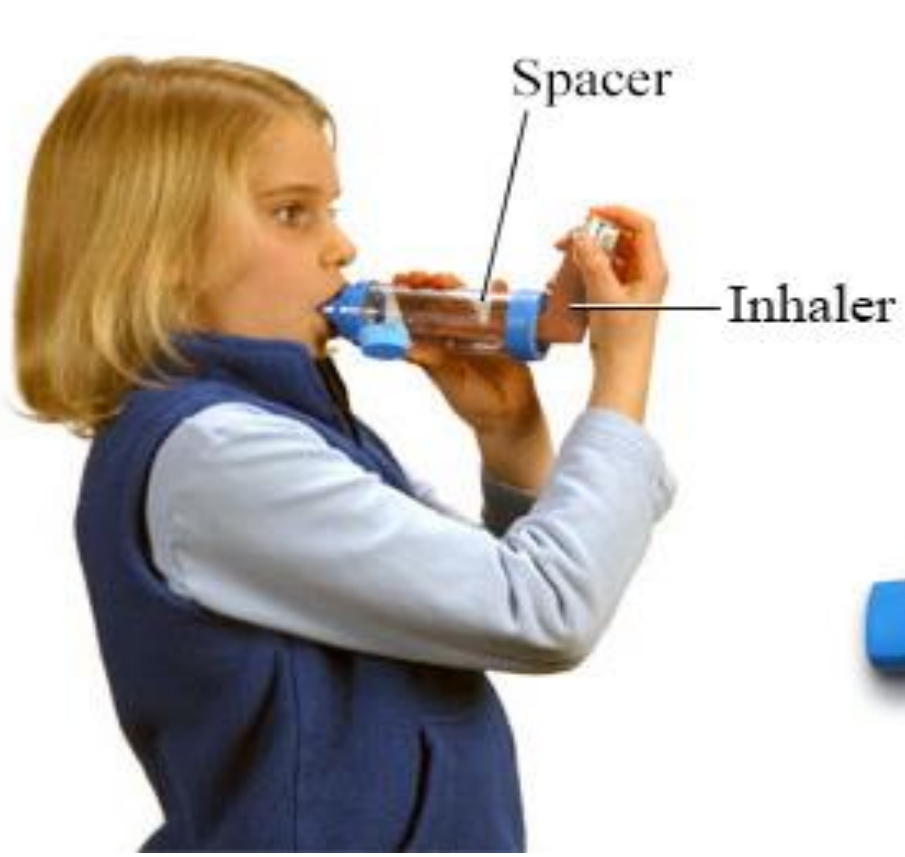
Side effects:

1- Oropharyngeal candidiasis

2- Dysphonia

Using of spacer and mouth rinsing decrease local side effects

3- Systemic side effects especially, in children and with high doses



Inhaler

Spacer

2- Oral :

Drugs: prednisone or prednisolone

- Typically: can be used for 5 days with no need for tapering

Indications:

- As maintenance therapy in acute severe asthma and status asthmaticus

3- **Intravenous**

- e.g. Methylprednisolone, hydrocortisone, dexamethasone
- IV route used in acute severe asthma (failure of bronchodilators) and status asthmaticus

Leukotrienes pathway modifiers

- **Leukotrienes receptor antagonists**

Montelukast, Zafirlukast

- **Leukotriene synthesis inhibitors**

  Zileuton

Leukotrienes receptors antagonists

- **Montelukast, Zafirlukast**

Both are having similar action and clinical uses

- **Mechanism of action**

Competitively block the common cysteinyl – Leukotrienes (C4 , D4 and E4) receptors in respiratory tract so preventing their bronchoconstriction effect

- They are given orally

Clinical uses

1. Alternative for inhaled glucocorticoid as prophylactic therapy for mild, moderate asthma
2. Prevention of aspirin – induced asthma

- Not used for terminating of acute asthma (they prevent bronchoconstriction rather than dilate the already constricted bronchi)

Side effects

- headache, rashes, muscle pain, eosinophilia.

Leukotrienes synthesis inhibitors

Zileuton is the only commercially available inhibitor of the 5-Lipoxygenase pathway

Clinical uses

Management of chronic, persistent asthma

Side effects

Headache (10%), elevated liver enzymes

Mast cell stabilizers

- **Na-chromoglycate and Nedocromil-Na**

- Reduce hyper-reactivity of the bronchial tree, prevent further attacks
- Prevent eosinophilic and neutrophilic chemotaxis
- Stabilize the mast cell of the bronchial airway
- Reduce the irritation of airway nerve endings
- There **is no bronchodilator effect**
- They are given by inhalation in asthma

Clinical uses

1. Prophylaxis in allergic and exercise-induced bronchial asthma.
2. Allergic rhinitis
3. Allergic conjunctivitis

Side effects: cough, throat irritation.

Ketotifen

- H_1 blocker (antihistamine) and mast cell stabilizer
- prevent degranulation of mast cells and release of inflammatory mediators in response to stimuli.
- It is **not a bronchodilator**.
- **Use**: long-term prophylaxis of allergic asthma

Bronchodilators

1. Selective β2 agonists
2. Xanthine derivatives
3. Anticholinergics

B_2 agonists

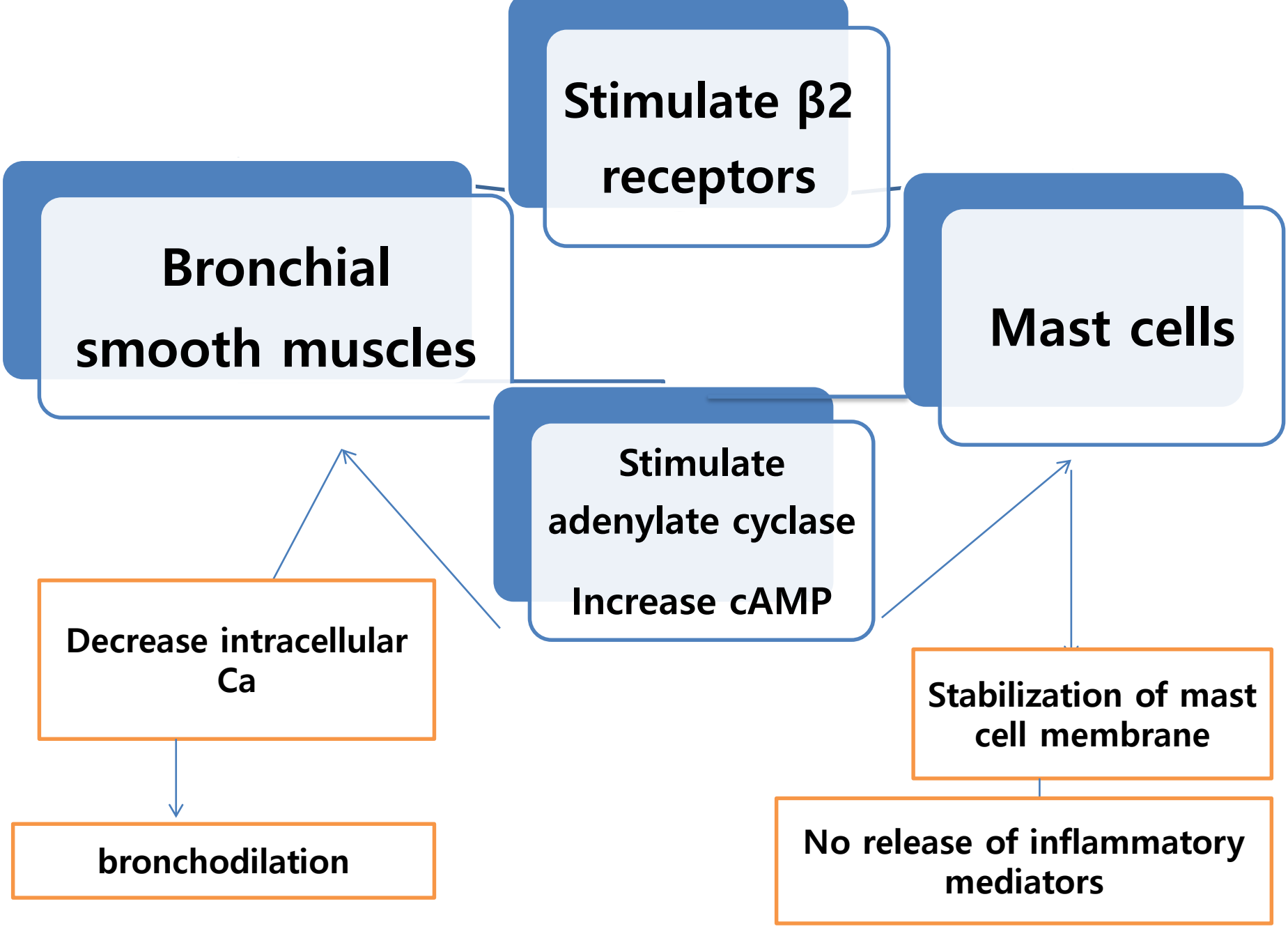
1. **Short-acting β2 adrenergic receptor agonists (Salbutamol , terbutaline)**
2. **Long-acting β2 adrenergic receptor agonists (Salmeterol; formoterol)**

Selective B2 Agonists

Mechanisms of Action

1) Stimulate ß2 receptors of bronchial smooth muscle--Stimulation of Adenylate cyclase---Increase intracellular cAMP----Smooth muscle relaxation ➞ Bronchodilatation

2) Act on the ß2 receptor of the mast cells--increase c-AMP production ➞ Stabilization of the mast cell membrane ➞No inflammatory mediators release ➞ No bronchoconstriction


Stimulate β2 receptors
Bronchial smooth muscles
Mast cells
Stimulate adenylate cyclase
Increase cAMP
Decrease intracellular Ca
bronchodilation
Stabilization of mast cell membrane
No release of inflammatory mediators

Salbutamol

- Can be administered orally, i.v. or by inhalation
- Bronchodilatation is immediate when given by inhalation
- Inhaled salbutamol is the drug of choice for acute bronchial asthma and for rapid prophylaxis against exercise-induced asthma
- Duration of action is short (4 hours)

It is used only on need because continuous use leads to down- regulation of bronchial β_2 receptors results in tolerance (tachyphylaxis).

Salmeterol

- Only administered by **inhalation**.
- It is **not** effective in acute attack because it has a slow onset of action (20 minutes).
- It has as a **long duration of 12 hours** because it is a highly lipid soluble as it contains a lipophilic side chain. This permits it to dissolve in the smooth muscle cell membrane adjacent to B2 receptor, then released slowly to act on receptors

- **Salmeterol is used for: <u>long term prophylaxis of bronchial asthma</u>**
- Since corticosteroids increase sensitivity of β2 receptors to β2 agonists, they may be given together
- Tolerance for salmeterol does not occur

Side effects of B2 agonist :

- ✓ **Tachycardia and tachyarrhythmia (due to stimulation of cardiac B1 receptors)**
- ✓ **Hypokalaemia, hyperglycemia and tremor due to stimulation of B2 receptors**

Quick review

25 year old asthmatic patient is complaining of severe shortness of breath and wheeze

What is the drug of choice?

Inhaled antimuscarinic bronchodilators

ex. lpratropium, oxitropium, tiotropium

- Anticholinergics cause bronchodilatation

by blocking muscarinic receptors

- Cannot be given orally, only by inhalation

(achieve high concentrations in the bronchial air way.

- Less systemic effect because they are

permanently charged so poorly absorbed after inhalation from lungs or GIT.

Clinical uses

1) Adjuvant to ß2 receptor agonists in acute asthma and status ashmaticus

2) Chronic obstructive pulmonary diseases (COPD)

Xanthine derivatives

Theophylline, Aminophylline

Mechanisms of Action

Inhibit phosphodiasterase enzyme PD4 that degrade c-AMP, c- AMP accumulate in the bronchial smooth muscle and causes bronchodilatation.

Increase c-AMP production ➞Stabilization of the mast cell membrane ➞No inflammatory mediators release ➞No bronchoconstriction

B2 agonist
Stimulate β2 receptors

Bronchial smooth muscles

Stimulate adenylate cyclase

Mast cells

Increase cAMP

Decrease intracellular Ca

bronchodilation

Inhibit PD-4

Xanthine deri.

Stabilization of mast cell membrane

No release of inflammatory mediators

3-Block adenosine receptor, prevents adenosine to cause contraction of the bronchial smooth muscle.

Pharmacological effects:

- ✓ Lung—bronchodilation
- ✓ CNS— stimulation, excitement, convulsions.
- ✓ CVS -positive ionotropic and chronotropic effects

In high level—toxicity— fatal cardiac arrhythmia

- ✓ Kidney— diuretic action, decrease

Na reabsorption in proximal tubules

- ✓ GIT—⬆gastric acid and pepsin secretion , vomiting

- **Theophylline is the prototype, it is water insoluble**
- **Given orally for chronic asthma, COPD**
- **Aminophyiline**
- **Water soluble salt prepared by mixing theophylline with Ethylene di-amine.**
- **Given intravenously in acute asthma and status asthmaticus.**

Total i.v. loading dose should be given slowly (**at least in 20minutes) to avoid CNS and CVS side effects**, resulted from exposure of heart and brain to high concentrations before drug distribution is complete

The loading dose **should be avoided** in any patient who is already taking, methyl xanthine preparation i.e. Oral theophylline or enzyme inhibitor drugs (always enquire about this before injecting)

Why theophylline require serum level monitoring TDM

1) Wide spreads pharmacological action

2) Low therapeutic index

Therapeutic blood level is 5-15mg/L.

The CNS and CVS side effects may occur in >20mg/L

3) Marked inter-individual variation in rate of metabolism ie . It is slowly in **elderly > 60 years**, **premature infant, obese, patients with heart failure and those with liver cirrhosis**

4) enzyme saturable at **therapeutic doses**, metabolism follows **zero order kinetic**.

4) Dose need to be reduced with enzyme inhibitors as erythromycin. ciprofloxacin, allopurinol and contraceptive pills.

Side effects

1. **CNS: tremor, anxiety, insomnia, restlessness, convulsions**
2. **CVS: hypotension, ventricular arrhythmias, ventricular fibrillation, cardiac arrest and death**
3. **GIT: nausea and vomiting**
4. **Metabolic: hypokalaemia**

Advantages of inhalation route in general:

- Achieve maximum local concentration and response, so lower doses are needed
- Less systemic absorption so less systemic side effects

Types of inhalation devices:

- Metered dose inhaler, dry powder or aerosoles
- Nebulizer

Drawbacks of inhalation route

Improper use of inhaler can result in a large fraction (approximately 80-90 %) of inhaled drug to be deposited in the oropharynx rather than bronchial smooth muscle or swallowed, excreted and/or resulted in systemic or local side effects.

To avoid this

1) The patient should be instructed to coordinate activation of the inhaler with deep, slow inspiration and then hold breath for few minutes.

2) Spacer (chamber interposed between the inhaler and patient mouth) to act as an aerosol reservoir that improve drug delivery to airways and reduce impaction of drug particles in oropharynx and improve inhaled to swallowed drug ratio

Quick-relief medications

- ✓ **Inhaled short-acting β_2-agonists (SABAs)**
- ✓ **Anticholinergics**
- ✓ **Systemic corticosteroids**
- ✓ **Intravenous aminophylline**

for refractory cases

- ✓ **Magnesium sulfate**

Thank You