ASTHMA

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Asthma

Chronic inflammatory disorder of small airways characterized by:

1. **Airway narrowing (obstruction):** Bronchospasm, submucosal edema, Increased mucus production and mucus plugging.
2. **Airway hyper-responsiveness**: An exaggerated broncho-constrictor response to wide range of stimuli.
3. **Airway inflammation:** mast cells and others inflammatory cell (eosinophil, macrophages etc)

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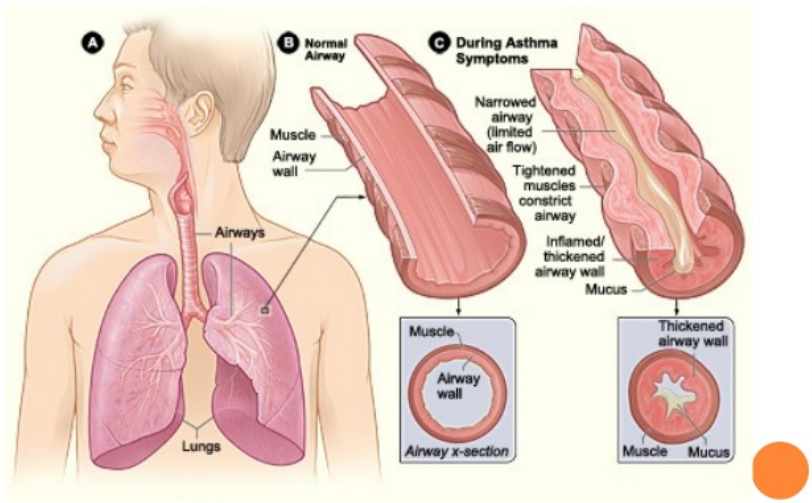

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Drugs Used for asthma are

1. Bronchodilators
   a. Sympathomimetics: Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol, Adrenaline, Ephedrine
   b. Methylxanthines: Theophylline, Aminophylline
   c. Anticholinergics (muscarnic receptor antagonist): Ipratropium bromide, Tiotropium bromide
2. Leukotriene antagonists: Montelukast, Zafirlukast
3. Mast cell stabilizers: Sodium cromoglycate, ketotifen, Nedocromil
4. Corticosteroids
   a. Systemic: Hydrocortosone, Prednisolone and others
   b. Inhalational: Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide
5. Anti-IgE antibody: Omalizumab

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Bronchodilators

- act primarily on airway smooth muscle to reverse the bronchoconstriction of asthma.
- rapid relief of symptoms but no effect on the underlying inflammatory process.
- are not sufficient to control asthma in patients with persistent symptoms.
- Three classes of bronchodilator in current use:

1) β2 adrenergic agonists,
2) anticholinergics, and
3) Theophylline.

- β2 agonists are the most effective.

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Sympathomimetics (β2 Adrenergic Drugs)

- stimulate the beta-receptor, increasing the cAMP concentration in smooth muscle and causing bronchodilatation.
- relaxes the bronchial smooth muscle without affecting cardiac function.
- In higher doses selective β2 agonist increasing the heart rate by stimulating the cardiac β1-receptor.
- The selective β2 agonist produce **hypertension** to patient those receiving digitalis.
- They are fastest acting bronchodilator when inhaled.
- Types

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

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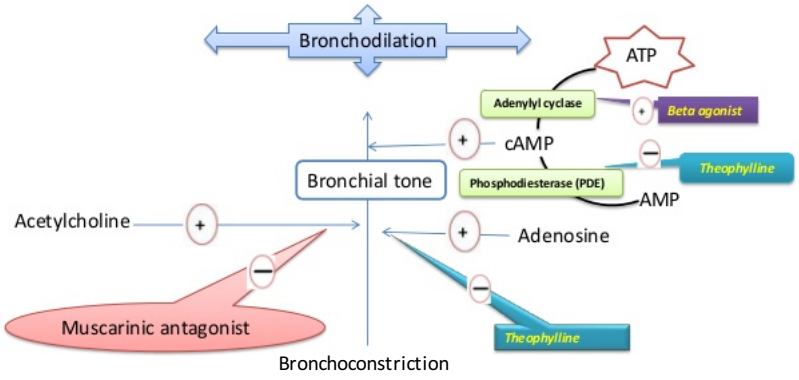
Mechanism of action of Bronchodilator



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Salbutamol

- Selective β2 agonists with less cardiac side effects
- Inhaled salbutamol produce bronchodilation within 5-min and the action lasts for 2-4 h.
- Used for acute asthmatic attack; Not suitable for prophylaxis
- Side effect: Palpitation, restlessness, nervousness, throat irritation and ankle edema (due to sodium retention)
- Metabolism: metabolized in gut; oral bioavailability is 50%.
- Duration of action: oral salbutamol acts 4-6 h
- Dose: 2-4 mg/ oral; 0.25- 0.5 mg/ s.c.; 100-200 µg by inhalation

Terbutaline

- Similar to salbutamol; regular use dose not reduce bronchial hyper-reactivity
- Dose: 5 mg/ oral; 0.25 mg s.c.; 250 µg by inhalation

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Bambuterol

- Biscarbamate ester of prodrug of terbutaline
- Slowly hydrolyzed in plasma and lung by pseudocholinesterase to release the active drug over 24 h.
- Used in chronic bronchial asthma in a singe evening dose of 10-20 mg/ oral.

Salmeterol

- First long acting selective β2 agonists with slow onset of action
- Twice daily for maintain the therapy/ nocturnal asthma, but not for acute asthma
- Concurrent use of inhaled glucocorticoid with salmeterol is advised for patient with persistent asthma.
- COPD: equivalent to inhaled anticholinergics in COPD.

Formoterol

- Long acting selective β2 agonists, which acts 12 h when inhaled.
- Compare to salmeterol, it has a faster onset of action (with in 10 min)
- Dose: 12-24 µg by inhalation twice daily.

Side effect: Palpitation, tachycardia, tremor, restlessness, nervousness, throat irritation and ankle edema

Tolerance

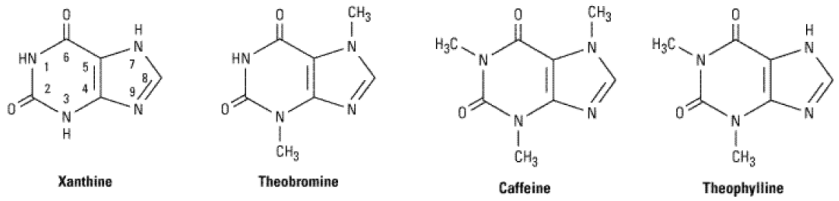
- Regular use of β2 agonists leads to diminished responsiveness
- May be due to down regulation of its receptor
- May be prevented by concomitant administration of ICS .

Nursing Consideration

- Take vital sign; BP and pulse; if elevated consult to physician.
- Notify patient that tremor and tachycardia may occur.
- Educate patient using inhaler and nebulizer

Methyxanthines

- Three important methylxanthines are theophylline, theobromine and Caffeine.
- Major source tea, cocoa and coffee respectively.
- Theophylline and its derivatives are most commonly used for the treatment of COPD and asthma.



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MOA of Methylxanthines (Theophyline)

- inhibits cyclic nucleotide phosphodiesterase (PDEs), thereby preventing conversion of cAMP to 5'-AMP. Inhibition of PDEs will lead to an accumulation of intracellular cAMP. Bronchodilatation, cardiac stimulation and vasodilatation occur when cAMP level rises in the concerned cells.

- is a competitive antagonist at adenosine receptors. Adenosine can cause bronchoconstriction in asthmatics and potentiate immunologically induced mediator release from human lung mast cells. Methylxanthines inhibits the adenosine action thereby causing bronchodilatation

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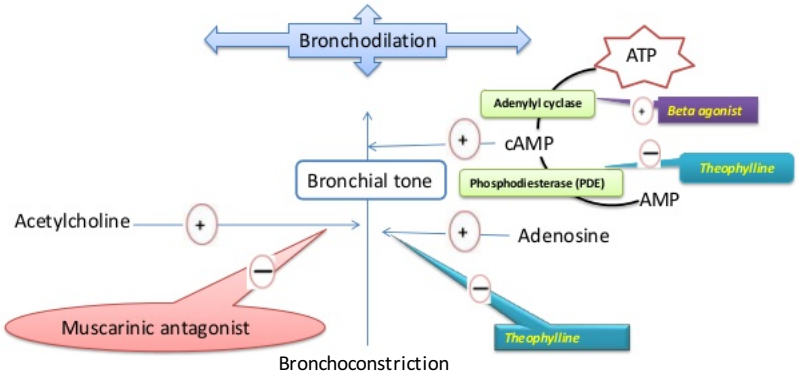
Mechanism of action of Bronchodilator



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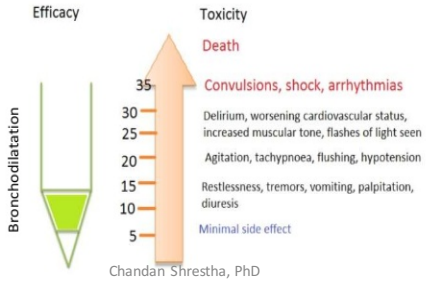
Adverse effects

- Narrow margin of safety
- Adverse effects occur in a dose related manner.
- Primarily referable to GIT, CVS and CNS.
- GI upset: nausea, vomiting headache
- Palpitation, restlessness, tachycardia
- High concentration: arrhythmia, seizures



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Anticholinergics (Muscuranic receptor antagonist)
Ipratopium/Tiotropium (derivative of atropine)

- Parasympathetic activation/ release of acetylcholine (ACh) cause bronchoconstriction and increase mucus secretion.
- Blocking the action of ACh by anticholinergic drugs produce bronchodilation and also reduce the volume of respiratory secretion.
- Less effective than sympathomimetic.
- Side effect: dry mouth; in elderly patients, urinary retention and glaucoma may also observed.

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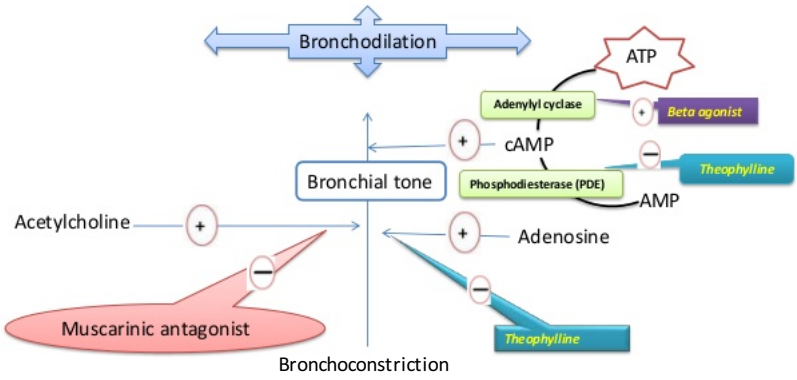
Mechanism of action of Bronchodilator



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Corticosteroids

- are not bronchodilator; benefit by reducing bronchial hyperreactivity, mucosal edema and by suppressing inflammatory response.

Inhaled steroids
(Beclomethasone dipropionate, Budenoside and Fluticasone)

- High topical and low systemic activity (due to poor absorption/ marked fast pass metabolism).
- Indicated when β2 agonist are required almost daily.
- High dose inhaled steroids are beneficial for advanced COPD with frequent exacerbations.
- Inhaled steroids produce less adverse effect as they are partially absorbed. [hoarseness of voice and oral candidiasis]
- This can be minimized by use of use of a large-volume spacer device, gargling after every dose.

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Corticosteroids

Systemic steroid therapy (Prednisolone)
Sever chronic asthma: Not controlled by bronchodilator and inhaled steroids.
Status asthmaticus/ acute asthma exacerbation

Oral glucocorticoids have systemic AEs and are usually reserved for patients with severe persistent asthma. (Systemic side effects, including truncal obesity, bruising, osteoporosis, diabetes, hypertension, gastric ulceration, proximal myopathy, depression)

Tapering dose

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Leukotriene antagonists
Montelukast, Zafirlukast

- Both are having similar action and clinical utility
- Block the cys-LT1 mediated bronchoconstriction, increased vascular permeability and recruitment of eosinophils.
- Alternative for inhaled glucocorticoids.
- Prophylactic therapy for mild, moderate asthma; not used for terminating asthma.
- Both are very safe drugs and ADRs are few (headache, rashes)
- Well absorbed orally, highly plasma protein bound and metabolized by CYP 2C9.
- Plasma $t_{1/2}$ of montelukast is 3-6 h, while that of zafirlukast is 8-12 h.
- Dose: Montelukast 10 mg OD, Zafirlukast 20 mg BD

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Mast cell stabilizers
Sodium cromoglycate

- Inhibits degranulation of mast cell by trigger stimuli and prevent the release of mediators from mast cells.
- Long time therapy reduces cellular inflammatory response.
- It is not histamine antagonist/ bronchodilator- ineffective in asthmatic attack.

Use

1. Bronchial asthma: as a long term prophylactic in patients not adequately controlled by inhaled bronchodilators.
2. Allergic rhinitis: not nasal decongestant, but regular prophylactic use as a nasal spray produces symptomatic improvement in many patients
3. Allergic conjunctivitis: Regular use as eye drops is beneficial in some chronic cases

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Anti-IgE antibody: Omalizumab

- recombinant DNA-derived monoclonal antibody
- Blocking antibody that neutralize circulating IgE thus inhibits IgE mediated reaction.
- Omalizumab may be particularly useful for treatment of moderate to severe allergic asthma in patients who are poorly controlled with conventional therapy.
- Due to the high cost of the drug, limitations on dosage, and limited clinical trial data, it is not currently used as first line therapy.

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Managements

- cannot be cured, but appropriate management can control the disorder and enable people to enjoy a good quality of life

1. Prevention (Identification of trigger)
2. Treatment
   - Anti inflammatory (corticosteroids); and
   - Bronchodilators

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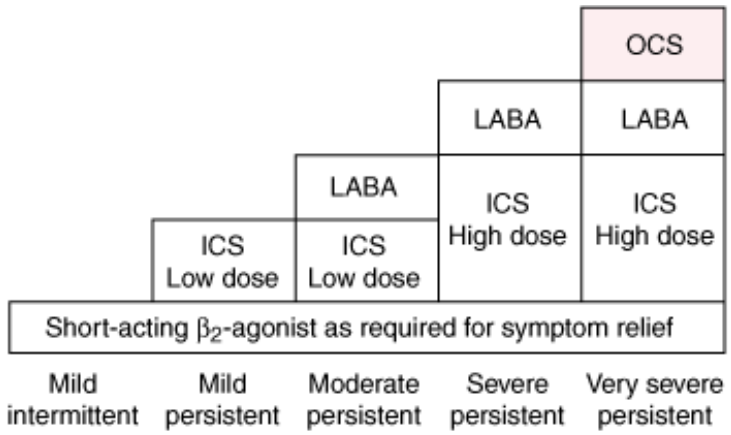

Step-wise approach to asthma therapy according to the severity of asthma and ability to control symptoms. ICS, inhaled corticosteroid; LABA, long-acting $_2$-agonists; OCS, oral corticosteroid.

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Chronic Obstructive Pulmonary Diseases (COPD)

- Includes

i. Chronic bronchitis: cough associated with inflammation of the bronchioles

ii. Emphysema: permanent destruction and enlargement of the airspaces distal to the bronchioles

- COPDs results airway obstruction, dyspnea, ↓ blood O_2 concentrations and ↑ blood CO_2 concentrations
- Risk factor of COPD: Smoking and old age
- Treatment

1. Bronchodilators and long time oxygen therapy.
2. Antibiotics can be used to treat acute exacerbations caused by bacterial infections.

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