7. Pharmacology of Drug Acting on Respiratory Tract

Drugs used in asthma and COPD, mucolytics, expectorants, antitussives, nasal decongestants.

Mucolytics, Expectorents and antitussives.

a)Mucolytics- These are the agents which decrease the viscosity of the sputum (thick mucus). This helps in easy expectoration. E.g. Acetylcysteine, carbocystein, bromohexine, ambroxol and pancreatic dornase.

Acetylcysteine- It is a derivative of amino acid cysteine. It decreases the viscosity of bronchial secretions by splitting of disulphide bonds in mucoproteins. This results in thinning the mucus, making it easier to be removed from the body by coughing. Another effect of acetylcysteine is seen in the treatment of acetaminophen (paracetamol) poisoning. When acetaminophen is ingested in toxic levels, it will bind to glutathione, resulting in liver damage and the production of abnormal hemoglobin. Acetylcysteine provides an alternate substance for the acetaminophen to bind to, resulting in minimizing liver damage.

It can be given as an aerosol or directly instilled into the respiratory tract.

Prep- Mucomix 200mg /ml in 1,2,3,5ml amps.

ADRs- Bronchospasm, fever, nausea and vomiting.

Bromohexine- It is a derivative of the alkaloid vasicine obtained from Vasaka plant. Bromhexine is a mucolytic. It liquefies and reduces the viscosity of sputum in the respiratory tract. It liquefies the viscid sputum by depolymerization of mucopolysaccharides directly as well as by liberating lysosomal enzymes.

ADRs- Rhinorrhoea (It is a condition where of mucus fluid), lacrimation, gastric irritation and hypersensitivity.

Preparations- Bromohexine 8mg tab, 4mg/5ml elixer.

Ambroxol is the active metabolite of bromohexine.Dose-15-30mg TID.

Pancreatic dornase- It is a stabilized deneoxyribonuclease preparation obtained from beef/bovine pancreas. It decreases the viscosity of the sputum. The thick gelatinous sputum may block the respiratory tract. This thick sputum changes to thin easily removable fluid. The pancreatic dornase is administered by inhalation in aerosol form.

Uses of mucolytics - Acute and chronic bronchitis, bronchiectasis (Bronchiectasis is a chronic condition where the walls of the bronchi are thickened from inflammation and infection). If the condition is present at birth, it is called congenital bronchiectasis. If it develops later in life, it is called acquired bronchiectasis), bronchial asthma, tuberculosis, dry cough.

b) Expectorants (mucokinetics) – These are a class of drugs which aid in the clearance of mucus from the airways, lungs, bronchi and trachea. These drugs increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

a)Directly acting-Ipecacuanha, Ammonium chloride, Ammonium bicarbonate, Guaifenesin, Senega, Squill, Terpine hydrate, Sodium iodide and Potassium iodide.

b)Mucolytics- as above

Ipecacuanha- It is a plant drug. On larger doses it is used as an emetic and on smaller doses it is used as an expectorant. It is a herbal medicine obtained from the roots of the plant *Cephaelis ipecacuanha*.

Ammonium chloride- Ammonium chloride is used as an expectorant in cough medicine. Its expectorant action is caused by irritative action on the bronchial mucosa, which causes the production of excess respiratory fluid, which is easier to cough up.

Ammonium bicarbonate- It is used as an expectorent (promoting the discharge of phlegm or other fluids from the respiratory tract. Phlegm is the thick viscous substance secreted by the mucous membranes of the respiratory passages, especially in excess quantities during a cold.

Guaifenesin- Guaifenesin (glyceryl guaicolate) is an expectorant drug sold over the counter and usually taken orally for promoting the discharge of phlegm from the respiratory passageways in acute respiratory tract infections.

Senega- It is a plant drug (polygala senega) used as an expectorant.

Squill- It is a plant extract has mild expectorant effect.

Terpine hydrate- It is derived from the oil of turpentine, eucalyptus oil. It is also used as an expectorant.

Sodium iodide- Its presence in the secretions cause irritation and initiate coughing reflex. It has saline action also. It is also is used as an antiseptic and in the treatment of hyperthyroidism.

Dose- 300mg TID.

ADRs- Iodism, rhinitis (inflammation and irritation of some internal areas of the nose), conjunctivitis, swollen eyelids, lacrimation, headache, skin rashes, hypothyroidism.

CI- In pregnancy, impaired renal function, hyperkalemia, hypersensitivity to iodine.

Guaiacol is a naturally occurring organic compound; this colorless aromatic oil is obtained from wood creosote. Guaiacol is produced industrially by methylation of catechol. Guaiacol and its derivatives e.g. guaiphenesin are used medicinally as expectorants. Tolu balsum (0.3-0.5g), vasaka syrup (2-4ml), terpin hydrate (0.1-1g) are also used as expectorants. **d) Antitussives** (Cough centre suppressents)- They inhibit the medullary cough center and thereby inhibit the coughing reflex. They should be used only in non- in productive cough.

i)Opioids- Codeine, pholcodeine, ethyl morphine, morphine.

ii)Non opioids- Noscapine, dextromethorphan.

iii) Antihistaminics.-Chlopheniramine, diphenhydramine, promethazine.

i)Opioids- Codeine- It has anti-tussive action at a lower dose-10mg. At this dose ADRs are less. It causes the release of histamine, this leads to constipation. Hence it is contraindicated in asthma.

Dose -10-30mg TID.

Pholcodeine has no analgesic or addiction property. It has prolonged antitussive action. Dose-10-15mg.

ii)Non opioids-

Noscapine-It is a non opioid. Therefore it has no drawbacks of opioids. But it causes histamine release and bronchospasm. Dose-15mg TID

Dextromethorphan- It is a synthetic drug having anti-tussive action. Its action is not through opioid receptors. Dizziness and ataxia (ataxia means lack of coordination while performing voluntary movements) are the only ADR.

iii)Antihistaminics.-Chlopheniramine, diphenhydramine, promethazine

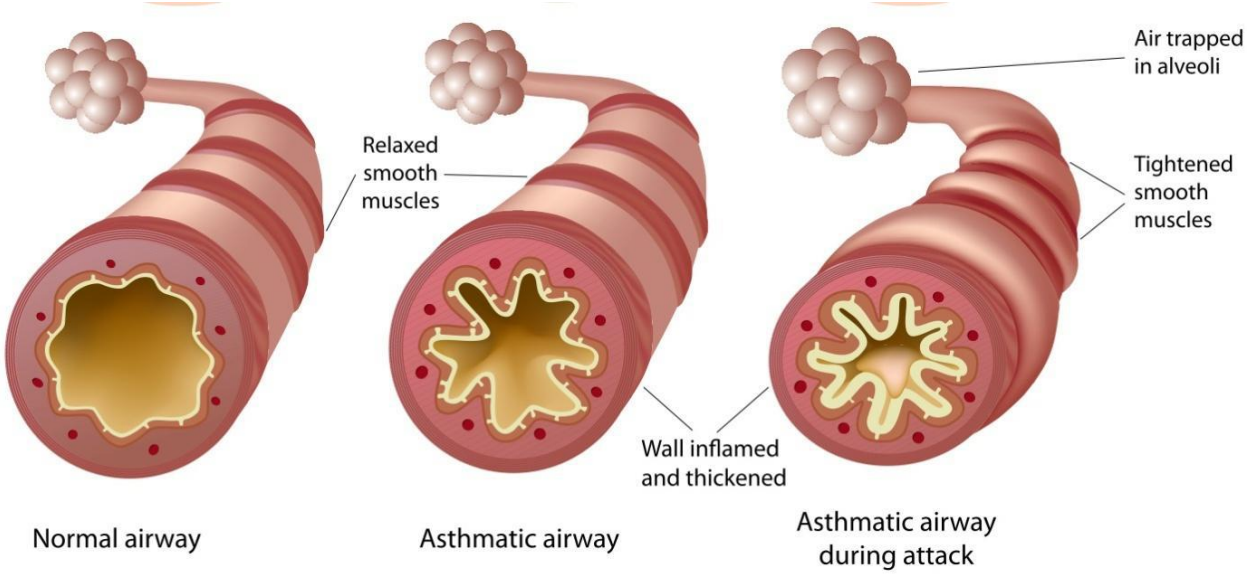
These are the H1 receptor antagonists. These are also having anti-tussive effect. Antihistamines antagonize the action of histamine. This action may be useful in patients with cough due to allergic conditions.

Uses of central cough suppressants- These drugs should be used in non-productive, dry, irritant type of cough. Cough suppression is necessary if cough is disturbing sleep or when coughing is hazardous- as in hernia, piles, after eye surgery, cardiac illness.

Drugs used in asthma and COPD.

Asthma- It is a chronic pulmonary condition characterized by chronic inflammation of the respiratory tubes, narrowing of air tubes, increased secretions, mucosal edema, mucous plugging and bronchoconstriction.

The airways of asthma patients are hypersensitive to certain triggers (stimuli). In response to exposure of these triggers causes bronchoconstriction followed by inflammation. This leads to further narrowing of the airways and excessive mucus production. This affects the normal breathing.



Drugs used in asthma-

1.Bronchodilators- a.Sympathomimetics- Adrenaline, ephedrine, isoprenaline, salbutamol, terbutaline.
b.Methylxanthenes- Theophylline, aminophilline, choline theophilline, hydroxyl ethyl theophiline.
c.Anticholinergics- Atropine methonitrate, ipratropium bromide, tiotropium bromide.
2.Leukotriene antagonists- Montelukast, Zafirlukast.
3.Mast cell stabilizers- Sodium cromoglycate, nedocromil.
4.Corticosteroids-
a.Systemic- Hydrocortisone, prednisolone.
b.Inhalational- Beclamethasone dipropionate, fluticasone proprionate, flunisolide.
1.Bronchodilators- a.Sympathomimetics- Adrenaline, ephedrine, isoprenaline, salbutamol, terbutaline.
b.Methylxanthenes- Theophylline, aminophilline, choline theophilline, hydroxyl ethyl theophilline.
Sympathomimetics-mechanism- Adrenaline binds to beta 2 receptors. These receptors are G protein coupled receptors expressed on the bronchial smooth muscles. When adrenaline binds to beta 2 receptors (Gs type), the dissociated α-GTP binds to adenylyl cyclase (AC) leading to increased formation of cAMP. The mechanism of cAMP induced bronchial smooth muscle relaxation is not clear. The cAMP activates the protein kinases, which cause hyperpolarization by closing the influx of calcium and by stimulating the efflux of potassium from the smooth muscle. This relaxes the bronchial smooth muscle.

Adrenaline is alpha, beta 1, beta2 and beta 3 agonists. It has long lasting bronchodilatation effect. It also has nasal decongestant effect (alpha receptor). It is rarely used now because of its vasoconstriction effect and cardiac stimulant effect.

Ephedrine-It has α +β1 + β2 actions. It is a constituent of combination in older formulation. Because of low efficacy and frequent side effects, it is seldom used now.

Isoprenaline- It is a beta1, and beta2 agonists. Through beta 2 receptors it produces bronchodilatation effect. But its disadvantage is tachycardia due to its beta 1 receptor effects.

Salbutalol-It is beta 2 selective agonist. Hence cardiac side effects are less prominent. Inhaled salbutalol produces bronchodilatation within 5 min and the action lasts for 2-4h. It is used for the termination of asthma attacks. But it is not suitable for the prophylaxis of asthma. It undergoes presystemic metabolism in gut wall. Its oral bioavailability is 50%. Oral salbutamol acts for 4-6h, is longer acting and safer than isoprenaline.

ADRs- Muscle tremors (unintentional, rhythmic muscle movements), palpitation, throat irritation and ankle edema.

Preps- 2-4mg tab, 0.25 to 0.5mg inj im/sc, 100-200μg by inhalation.

Terbutaline- It is similar to salbutanol in properties and use.

b.Methyl xanthins- Theophilline is 1,3 dimethyl xanthine. Methyl xanthenes are used in asthma. But these drugs are not considered as first line drugs, used more often in COPD.

Pharmacological actions-

CNS- Caffeine and theophylline are CNS stimulants, primarily affect the higher centres.. They also stimulate vagal, respiratory and vasomotor centres. Higher doses cause nausea and vomiting due to gastric irritation and CTZ stimulation.

CVS- Methyl xanthines directly stimulate the heart and increase the force of heart contraction. But through vagal stimulation decrease the heart rate and force of heart contraction, hence the net effect is variable. Theophilline causes tachycardia, but caffeine decreases heart rate. Methyl xanthines cause dilatations of systemic blood vessels including coronary blood vessels. But cranial blood vessels get constricted. Hence they are indicated in migraine. Methyl xanthenes also increase systolic BP but decreases diastolic BP.

Smooth muscles- Relaxes the bronchial smooth muscles. They relax other smooth muscle also.

Kidney- They produces mild diuretic action by inhibiting the tubular reabsorption of sodium and water.

Skeletal muscles- Caffeine enhance the skeletal muscle contraction.

Stomach- They enhance the acid and pepsin secretion.

Metabolism- They increase BMR.

Mast cells and inflammatory cells- Theophylline inhibit the release of histamine and other mediators from the mast cells and activated inflammatory cells.

Mechanism of methylxanthines-

1. Competitive nonselective phosphodiesterase inhibitor. Which raises the intracellular cAMP, activates PKA, inhibits TNF-alpha and inhibits leukotriene synthesis and reduces inflammation.

2.Adenosine is a local hormone in CVS, CNS and other organs. Adenosine causes bronchoconstriction by interacting with adenosine receptors (A1, A2, A3). Methyl xanthins produces bronchodilatation by blocking these receptors.

ADME of theophilline- Well absorbed orally. It is well distributed in all the tissues. About 50% bound to plasma proteins. It crosses placenta and is secreted in milk. It is metabolized in the liver by demethylation and oxidation. The metabolites are eliminated through urine. About 10% of its free form is eliminated through urine.

ADRs- Theophylline has narrow margin of safety. Gastric pain (with oral), rectal inflammation (with suppositories), pain at the site with im inj. Convulsions, shock, arrhythmias, agitation, insomnia, nervousness, etc. Sudden iv inj causes pricordial pain (pain at the left chest muscles), syncope and even death.

T.Uses- Theophylline is used in bronchial asthma and COPD. It is also used to treat apnoea in premature infant.

Preparations- Theophilline 100, 200mg tab, capsules, aminophilline inj, hydroxyethyl theophylline (deriphillin).

c.Anticholinergics- Atropine methonitrate, ipratropium bromide, tiotropium bromide.

Atropinic drugs act by blocking M3 receptors located on the bronchial smooth muscles.M3 receptors belongs to G-protein coupled receptors (Gq type).

Uses- Atropinic drugs are indicated in COPD and prophylaxis of asthma.

d. Leucotriene antagonists- Montelukast, zafirlukast.

Cystenyl leucotriens (LTC4 and LTD4) are the important mediators in bronchial asthma. In allergic response these mediators bind to their receptors (leucotriene receptors) located on the bronchial smooth muscles causing bronchoconstriction.

Both montelukast, zafirlukast acts by blocking the leucotrine receptors. This leads to bronchodilation, decreases of capillary permeability, reduced eosinophil count in the sputum, reduced inflammation (antiasthmatic effects).

ADME- They are well absorbed orally. They bound to plasma proteins, metabolized by cytochrome enzymes of the liver. The metabolites are eliminated through urine.

Uses- Both montelukast, zafirlukast are indicated in prophylaxis of mild to moderate asthma.

ADRs- Headache and rashes.

e.Mast cell stabilizers- Sodium chromoglycate It is a synthetic chromone derivative which inhibits degranulation of mast cells by trigger stimuli. Release of mediators of asthma like histamine, LTs, PAF, interleukins etc from mast cells as well as other inflammatory cells is prevented. It is not a bronchodilator and does not antagonize bronchoconstrictor action of histamine, LTS, PAF, acetylcholine, etc.

ADME- Sodium chromoglycate is not absorbed orally. It is administered as an aerosol through metered dose inhaler delivering 1mg/ dose four times a day. Only small fraction of the inhaled drug is absorbed systemically. This is rapidly excreted unchanged in the urine.
Uses-1. It is used for the long term prophylaxis of bronchial asthma.
2.It is also indicated in allergic rhinitis and allergic conjunctivitis.

f.Corticosteroids- a.Systemic- Hydrocortisone, prednisolone.
b.Inhalational- Beclamethasone dipropionate, fluticasone proprionate, flunisolide.
These are also not bronchodilators. But they reduce the bronchial hyperactivity, mucosal edema, suppress inflammatory response to AG:AB reaction or other trigger stimuli. They give more relief in asthma than other antiasthmatic drugs, but long term systemic steroid therapy has its own adverse effects which may be worse than asthma itself. ADRs- Hyperglycaemia, muscular weakness, peptic ulceration, osteoporosis, glaucoma, growth retardation, foetal abnormalities, psychic distrubences,
Uses- Indicated in mild to severe asthma, COPD, status asthmaticus (severe type of asthma).

Nasal decongestants- Nasal congestion (stuffy nose)is the blockage of the nasal passages usually due to membranes lining the nose becoming swollen from inflamed blood vessels. Nasal decongestants target the discomfort directly.

Nasal decongestants are alpha agonists which on topical applications as dilute solution (0.05 to 0.1%) produce local vasoconstriction. The following are the drugs used as nasal decongestants.

1.Imidazole compounds- Naphazoline, xylometazoline, oxymetazoline.
2.Pseudoephidrine
3.Phenylpropanolamine.

Naphazoline- It is a sympathomimetic agent with marked alpha adrenergic activity. It reduces the nasal swelling (congestion) in the nasal membrane by causing vasoconstriction. The naphazoline binds to the alpha receptors expressed on the vascular smooth muscles membranes causing vasoconstriction. Alpha 1(α1) is a GPCR (Gq type). Naphazoline act by binding to the α1 receptors located on the vascular smooth muscles of the nasal mucosal membrane and through PLC, IP3, DAG, Calcium –Calmodulin pathway it causes vasoconstriction.

ADRs- Hypertension, cardiac arrhythmia. Uses- Used as nasal decongestant.

Pseudoephedrine- It is a sympathomimetic agent. It shrinks the blood vessels in the nasal mucosal membrane and reduces the nasal congestion (stuffy nose).

ADRs- Nervousness, excitability, dizziness, insomnia, stomach pain, etc.

Uses-It is used to treat nasal and sinus congestion. It is used to relieve nasal congestion due to common cold, hay fever or other upper respiratory allergies and nasal congestion associated with sinusitis.

Phenylpropanolamine- It is a sympathomimetic drug. It acts on both α and β adrenergic receptors. In India this drug was banned in the year 2011. In few countries in Europe, however, it is still available.