Pharmacology of Respiratory system

Nervous innervations of bronchial muscle

Parasympathatic stimulation	***Sympathatic stimulation***
Increase mucus production Smooth muscle constriction bronchoconstriction	Decrease mucus production Smooth muscle Relaxation bronchodilation

- **The intracellular mechanisms** that transmit signals from the nervous system to smooth muscle depend, in part, on changes in:

the intracellular concentration of

1- cyclic adenosine monophosphate (cAMP) → induces bronchodilation

2-cyclic guanosine monophosphate (cGMP) → induce bronchoconstriction.

- • The increased intracellular concentration of one of them is associated with a decreased concentration of the other.

Respiratory stimulants

These are drugs which quicken or deepen respiration by stimulating the respiratory centre in the medulla.

Uses:

1- Used in respiratory depression or respiratory failure as in case of poisoning with general anaesthetics, sedatives, or hypnotics.

2- Used to improve respiration during and after general anaesthesia.

3- Used in case of asphyxia.

Classification:

1) Reflex stimulants:

2) Direct stimulants:

1) Reflex respiratory stimulants:

- They are administered by inhalation. A good example is **ammonia gas** liberated from the stopper of a bottle of strong solution of ammonia, or from ammonium carbonate.
  MOA : Ammonia irritates the sensory nerve endings in the nose and causes reflex stimulation of the respiratory centre as well as the vasomotor centre, so improve respiration and circulation.

Direct respiratory stimulants:

They act by direct stimulation of the respiratory and vasomotor centers in the medulla, so improve respiration and circulation.

a-Analeptics:

- ***Doxapram hydrochloride*** is a CNS stimulant that is used primarily as a stimulant of the respiratory system. It used for stimulation of respiration during and after anaesthesia. It stimulates both, the respiratory centre in the medulla and chemoreceptors in the carotid arch.

- ***Picrotoxine*** is an alkaloid having a powerful respiratory stimulant effect. It is used to overcome depressed respiration in case of poisoning by narcotics. It is not given orally but given by intravenous injection. It is rarely used due to its toxic effect.

- ***Leptazole*** is a synthetic drug acts as picrotoxine but less toxic. It is given by intravenous injection to stimulate respiration in case of poisoning by barbiturates and alcohols.
- ***Coramine (nikthamide)*** is less potent and less toxic than picrotoxin with prolonged duration of action. It is given orally or by injection. It acts both directly on the respiratory centre and reflexly on chemoreceptors in carotid arch.
- ***Bemegride (megemide)*** is used mainly to antagonize the medullary depression due to over dose of
- barbiturates and other hypnotics.

B -Physiological stimulants:

Carbogen gas: It is a mixture of oxygen (90-95 %) and carbon dioxide (5-10 %).

Oxygen is the first essential of all life. It plays a critical role in the treatment of respiratory failure..

Carbon dioxide is a potent respiratory stimulant by acting directly on the respiratory centre in the medulla and reflexly on chemoreceptors in the carotid arch. Carbon dioxide in low concentrations (5-10%) stimulates both depth and rate of respiration, while higher concentrations depresses the respiration and may cause death. Methods of administering carbogen include oxygen cages, oxygen hoods, nasal cannula and endotracheal tube.

Uses of carbogen:

1- In the treatment of respiratory failure, hypoxia and asphyxia.

2- During severe pneumonia and pulmonary edema.

Mucolytics

Mucolytic are drugs which alter the structure of mucus to decrease its viscosity and therefore facilitate its removal from the respiratory tree by ciliary action and expectoration.

- ***Uses:***
- 1- Used in conditions associated with viscous pulmonary secretions such as are commonly associated with bronchitis, pneumonia and tuberculosis.
- 2- Used in combination with aerosolized antimicrobials to improve antibacterial penetration of infected mucus.

*Acetylcyst*ein

- It is effective following aerosolization, but more recently oral administration has become the preferred route because it cause reflex bronchoconstriction due to irritant-receptor stimulation.
- it is metabolized to sulfur-containing products, so it should be used cautiously in animals suffering from liver disease.

MOA: The **free sulfhydryl** group of acetylcystein breaks disulfide bonds in the **mucoprotein**. Smaller molecules are less viscid and easily removed by ciliary action.

Bromohexine

- of value in liquefaction of mucus by increasing its volume and decreasing its viscosity. It is given orally or parentrally for 7 days. ***Ambroxol*** is a metabolite of bromohexine and has similar actions.

MOA: It improves l**ysosomal function**, so lysosomal enzymes hydrolyze the **mucopolysaccharide** fibers of the mucus.

Expectorants

- Drugs that act on the bronchial glands to increase the volume of bronchial secretions and therefore help their removal by ciliary action and coughing.
- Uses: Expectorants are indicated when a productive (moist) cough is present as in cases of bronchitis and pneumonia.

Classification of expectorant

Alkaline	Nauseant	Direct
sodium or potassium citrate sodium, potassium or ammonium acetate **MOA:** orally and then converted into carbonates in tissues excreted through bronchial glands causing mild irritation of the secretory cells producing increased bronchial secretions.	**Plant:** Ipecacuanha (Ipecac.) Senega (Polygala): Squill (Scilla) , Tolu **Metalic:** Ammonium carbonate , Antimony potassium tartrate (Tartar emetic) **MOA:** irritating the sensory nerves of gastric mucous membrane so stimulate reflexly the bronchial glands to secrete more secretions	**Non inhalant direct expectorants** : such as potassium iodide and ammonium chloride **Inhalant direct expectorants(aromatic expectorants:** guaiacol, Tr. benzoin, eucalyptus oil, camphor, turpentine oil, etc **MOA:** excreted from the bronchial glands causing their irritation, so increasing bronchial secretion acting as expectorants

Bronchial asthma

Bronchoconstriction can result from 3 basic mechanisms:

1- Release of acetylcholine at parasympathetic nerve endings.

2- Release of histamine through an allergic mechanism.

3- Blockade of β_2-adrenergic receptors by drugs such as propranolol.

Bronchodilators

- Drugs which dilate bronchial muscles when they are contracted as in case of bronchial asthma

- ***Uses:***

1-Used to relieve bronchial asthma.

2-Used where there is suspicion of bronchial narrowing due to bronchial secretion as in cases of bronchitis and bronchopneumonia.

- **Classification:**

1-Adrenoceptor agonists

2-Antimuscarinic bronchodilators

3-Xanthine derivatives

β-receptor agonists

- β-receptor agonists are the most effective bronchodilators because they act as functional antagonists of bronchial contraction, regardless of the stimulus. They are equally effective in large and small airways.
- **MOA:** The interaction between a β-agonist and its receptor results in activation of adenylate cyclase on the inner cell membrane. Adenylate cyclase converts adenosine triphosphate (ATP) to cAMP, which in turn activate some enzymes that cause relaxation of bronchial smooth muscle.
- ***A) Non selective β-agonists:***
- Non selective β-agonists are capable of stimulation of both β_1 and β_2 receptors. They may cause adverse cardiac effects due to β_1 receptor stimulation. Aerosol administration reduces their adverse effects, since only β_2 receptors appear to line the airways. Inhaled bronchodilators are highly effective in severe asthma.
- ***Epinephrine*** It acts on α, β_1 and β_2 adrenergic receptors
- ***ephedrine*** It acts on α, β_1 and β_2 adrenergic receptors
- ***Isoprenaline (isoproterenol)*** It acts on β_1 and β_2 adrenergic receptors

B) Selective β-agonists:

They are capable of stimulation of β_2 receptors. Despite of minimum undesirable effects, few of these drugs have been used in animals.

Salbutamol (ventolin or albuterol) is a bronchodilator used to treat or prevent the symptoms of asthma. It produces bronchodilation through stimulation of β_2-adrenergic receptors in bronchial smooth muscle, thereby causing relaxation of bronchial muscle fibers. This action is manifested by an improvement in pulmonary function.

It can be given by oral, injection or by inhalation routes. The inhaled form of salbutamol is more effective and has a faster onset of action than the oral form, so used for acute asthma (given during attacks). Oral salbutamol is highly effective in chronic asthma (given before attacks). The drug may be inject

Methylxanthines:

- Include: Theophylline,
  Aminophylline and
  Etamiphylline.

- ***Mechanism of action:***

Phosphodiesterase-enzymes tend to promote bronchoconstriction because it inhibits cAMP in smooth muscle cells. Methylxanthines acts by inhibition of phosphodiesterase enzymes, so increase the concentration of cAMP in smooth muscle cells causing bronchodilation.

3) Anticholinergics

- **Atropine**
- **Ipratropium bromide**

- Effects of anticholinergics are confined to large airways. They are given orally or by injection and have a slower onset of action.

MOA:

Three types of muscarinic receptors have been identified in airways.

- M_3-receptors release acetylcholine,
- M_2- receptors block its release
- M_1-receptors on which, acetylcholine acts.

Anticholinergic drugs act by blocking the muscarinic receptors of the bronchial muscle, so antagonize the bronchoconstricting effect of acetylcholine.

Treatment of bronchial asthma:

1) Anti-inflammatory drugs:

Corticosteroids

ex: dexamethazone or betamethasone

2) Bronchodilators:

a) Short-acting β-adrenergic agonst

ex: **salbutamol**

b) Theophylline is used for asthma control, but not as the first choice of medications.

c) Ipratropium

Prophylaxis of bronchial asthma:

1) Anti-inflammatory drugs:

Corticosteroids

ex: dexamethazone or betamethasone

2) Bronchodilators:

a) long-acting β-adrenergic agonst

ex: **isoprenaline ; isoproterenol**

b) Theophylline

Antitussive Drugs (Cough suppressants or Cough Sedatives)
These are drugs which suppress coughing

MOA: Interfering with cough reflex either at the cough center or at the irritant receptors in the upper respiratory tract

Therapeutic uses: They are used in case of dry cough

1- Central antitussive

-Narcotic

Codeine - hydrocodone

-NON-narcotic

dextromethorphan

butorphanol tartarate

2-Prepheral antitussive

-Mucolytics

-expectorants

Decongestants

- ***Drugs which relieve symptoms associated with nasal congestion as runny nose & sneezing***

1) Sympathomimetic drugs,

i.e. α –adrenergic agonists as **ephedrine** and **phenylephrine**. Topical drugs (nasal sprays) act within minutes

***Mechanism of action*:**

1-Stimulation of α_2 receptors concentrated on the precapillary arterioles results in vasoconstriction, so blood flow to the nasal mucosal capillary bed is reduced. Consequently, congestion, excess extracellular fluid and nasal discharge are decreased.

2- Stimulation of α_1 receptors concentrated on the postcapillary venules results in vasoconstriction, so blood volume in the mucosa is reduced to relieve congestion.

- Oral treatment with sympathomimetic drugs can be associated with a number of adverse reactions as systemic vasoconstriction, hypertension tachycardia and urine retention.

2) Histamine (H_1) antagonists:

Antihistaminics reduces many of the symptoms commonly associated with allergies, including runny nose and sneezing. They can be administered in several different forms, including Liquid; nasal sprays and eye drops

ex; diphenhydramine

Newer antihistaminics **(chlorpheniramine)** are associated with minimal sedation.

- Antihistaminics act to block histaminic receptors (H_1 receptors) found on vascular smooth muscles from responding to histamine.

- Antihistaminics are effective for treatment of allergic rhinitis.