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Unit-IV

Pharmacology of Respiratory System - Part 2

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ANTI TUSSIVES

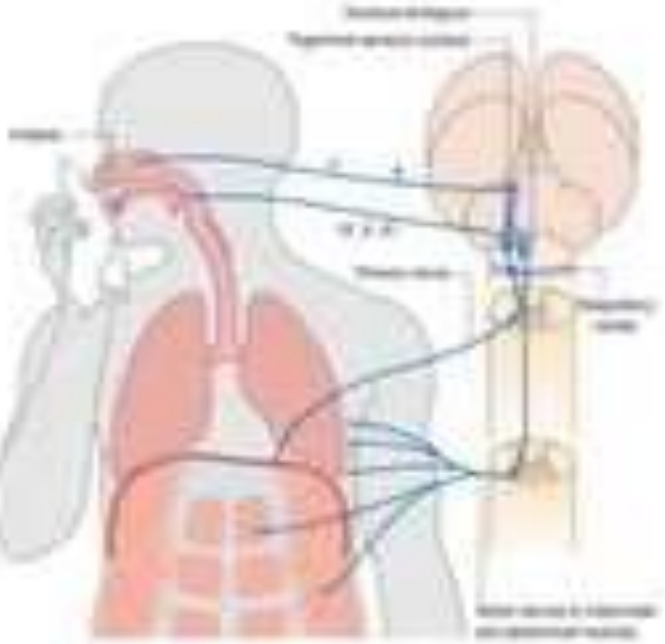
- Antitussives are agents that suppress coughing and are indicated when reducing cough frequency is needed,especially when the cough is dry and nonproductive.(ANTI-oppose ;TUSSIVES – related to cough).
- The mechanism by which the narcotic and nonnarcotic agents affect a cough's intensity and frequency depends on the principle site of action:

  - CNS depression of the cough center in the medulla(cough reflex)

  or

  - suppression of the nerve receptors within the respiratory tract.

Mechanism of cough



Stimulation of mechano-or chemoreceptors (throat, respiratory passages or stretch receptors in lungs)

⬇

Afferent impulses to cough center (medulla)

⬇

Efferent impulses via parasympathetic & motor nerves to diaphragm, intercostal muscles & lung

⬇

Increased contraction of diaghramatic, abdominal & intercostal (ribs) muscles ⇒**noisy expiration (cough)**

CLASSIFICATION OF ANTI TUSSIVES

- Opioids
- Non opioids
- Antihistamines
- Bronchodilators

OPIOIDS

CODEINE

- It is opium alkaloid more selective inhibiting the cough center, less potent than morphine.
- Suppresses cough for above 6 hours.
- Abuse liability is low.
- Adverse Effects: Constipation(common),higher doses can cause respiratory depression and drowsiness(especially in children).
- Average adult dosage is 10-30 mg every 4 to 5 hours.


Triprolidine Hydrochloride &
TOPCOFF-T
• ANTI ALLERGIC
• ANTI TUSSIVE
• FOR DRY COUGH

Ethyl morphine:-

- ✓similar to codeine and is less constipating.
- ✓Dose:10-15 mg.

Pholcodeine:-

✓ similar to codeine,long acting and non – addicting(12 hours).

✓Dose:10-15 mg.

NONOPIOIDS

Noscapine

- It depresses the cough center, non-narcotic, no analgesic or dependance inducing properties.
- Equipotent as codeine and is useful in spasmodic cough.
- Adverse effect:Headache and nausea(most common)

Dextromethorphan

- It is found in many cough and cold medications
- It acts on the CNS centre in the brain (medulla oblongata).
- It redues the urge to cough without having the sedative effects associated with opioids.

- Side effects:Dizziness,nausea,drowsiness.vomiting.
- Dosage:10-20 mg adult.

Chlophedianol

- It is a centrally acting antitussive with slow onset and longer duration of action.
- Side effects:Dryness of mouth,irritability.
- Dosage:20-40 mg.

Benzonatate

- It a local anesthetic,acts peripherally and surppresses the stretch receptors in the respiratory passages,lungs and pleura.
- Adverse effect:dizziness, dysphagia.

ANTIHISTAMINES

- Antihistamines are medications that help alleviate symptoms caused by histamines,a chemical released during allergic reactions.
- They are primarily used to treat allergies,colds and fever.
- Mechanism: Antihistamines block the H1 histamine receptors in the upper respiratory system.
- Other group of antihistamines are H2 blockers and they affect the cells in the gastrointestinal tract.
- Ex:-Diphenhydramine(15-25 mg),chloropheniramine (2-5 mg).

BRONCHODILATORS

- β2 –sympathomimetics, Methylxanthines,anticholinergics.
- Useful in controlling cough associated with bronchoconstriction.

PHARMACO

ANTI – ASTHMATIC DRUGS

ASTHMA

- Asthma is most common respiratory tract infection. It is the reversible obstruction of large and small airways.
- Bronchial asthma is characterized by hyper-responsiveness of tracheo-bronchial smooth muscle to a variety of stimuli, resulting in narrowing of air tubes, often accompanied by increased secretion ,mucosal edema and mucus plugging .

- **Asthma is a disease of airways that is characterized by spasmodic narrowing of the air passages.**

- ▪ It is an episodic air flow obstruction due to bronchospasm.
- ▪ The condition exhibits short or long spells of breathing difficulty along with dyspnoea, wheezing and cough.
- ▪ Usually small bronchioles and rarely medium sized bronchi are affected.
- ▪ Normally lumen of bronchial tree is wider during inspiration and narrowing during respiration.

- ▪ This tendency to narrow down is highly exaggerated in asthma and hence expiratory
- breathing difficulty is more prominent.
- ▪ It occurs at all ages but nearly 50% of cases develop it before the age of 10 years.
- ▪ Both sexes are equally affected in adults, but in youngsters, the male to female ratio
- is 2:1.

SYMPTOMS

- Shortness of breath
- Chest tightness or pain
- Wheezing when exhaling, which is a common sign of asthma in children
- Trouble sleeping caused by shortness of breath, coughing or wheezing
- Coughing or wheezing attacks that are worsened by a respiratory virus, such as a cold or the flu

CAUSES

- Airway narrowing takes place in response to some agents called allergens.
- Allergens – Pollens, dust, mites, exposure to cold air, some food materials
- ➢ Cigarette Smoking
- ➢ Air pollution
- ➢ Anxiety
- ➢ Upper respiratory tract infection
- ➢ Emotion stress
- ➢ Strenuous exercise

TYPES OF ASTHMA

- (Based on etiology)
- ***1. Extrinsic Asthma: (allergic)***
- ➢ Most common type of asthma.
- ➢ It usually starts in infancy or early adulthood.
- ➢ Most patients of this type of asthma have personal and/or family history of preceding allergic disease such as rhinitis, uriticaria or infantile eczema.
- ➢ This cause in presence of allergens **Eg: Theophylline**

- ***2. Intrinsic asthma (Idiosyncratic, non-atopic):***
- ➢ It develops later in adult life with absence of personal or family history of allergy.
- ➢ Most of these patients develop typical symptom complex after an upper respiratory tract infection by virus.
- ➢ They have many causes other than exposure to allergens.
- **Eg: Omalizumab (Xolair)**

- ***3. Mixed Type:***
- ➢ Many patients don't fit neatly into either of the two groups above and exhibit traits from both.

ANTI –ASTHMATIC DRUGS

- ▪ Drugs which are used in the treatment of Asthma or bronchial asthma are known as Anti-asthmatic drugs.

CLASSIFICATION

- ▪Bronchodilators
- ▪Leukotrienes Antagonists
- ▪Mast cell stabilizers
- ▪Corticosteroids
- ▪Anti IgE antibody

Bronchodilators

- Bronchodilators are a type of medication that make breathing easier by relaxing the muscles in the lungs and widening the airways .
- The 3 most widely used bronchodilators are: beta-2 agonists – like **salbutamol, salmeterol, formoterol and vilanterol.**

Leukotrienes Antagonists

- Leukotriene receptor antagonists (LTRAs) are a class of drugs that treat and prevent asthma and allergic rhinitis by blocking the effects of leukotrienes
- **What are leukotrienes?**
- Leukotrienes are inflammatory mediators that cause inflammation in the lungs and constriction of bronchial smooth muscle. They are produced from arachidonic acid by 5-lipoxygenase in inflammatory cells in the airways.

Mast cell stabilizers

- Mast cell stabilizers are medications that prevent mast cells from releasing inflammatory mediators, such as histamine, leukotrienes, and prostaglandins.

Corticosteroids

- Commonly referred to as steroids, corticosteroids are a type of anti-inflammatory drug.
- They are typically used to treat rheumatologic diseases, like rheumatoid arthritis, lupus or vasculitis.
- Specific corticosteroids include the medications **cortisone** and **prednisone**.

Anti IgE antibody

- Anti-immunoglobulin E (IgE) antibodies are used to treat allergic diseases by preventing the development of an allergic reaction.
- **Omalizumab (Xolair)** is an example of an anti-IgE antibody.

SALBUTAMOL

→Also known as Albuterol

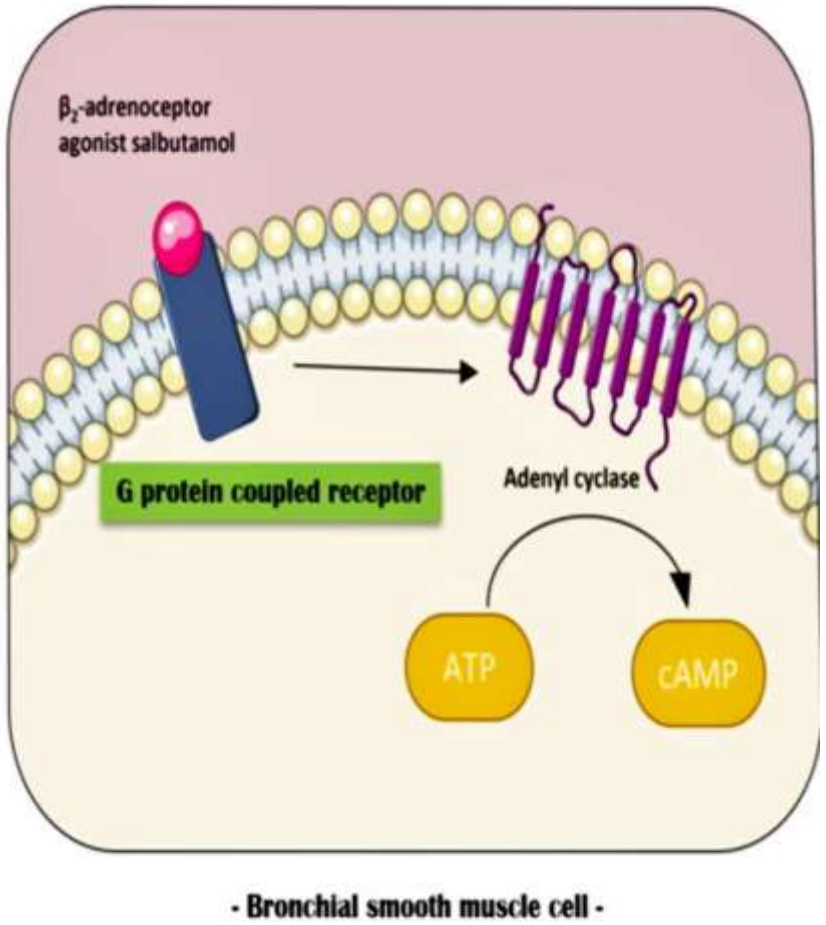
- Beta 2 – adrenergic receptor agonist
- Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and COPD.

- **ONSET OF ACTION:**
- <15 min (inhaled)
- <30 min (pills)
- **ELIMINATION HALF LIFE:**
- 3.8 to 6 hrs

MECHANISM OF ACTION

- Salbutamol is a selective B2-adrenoceptor stimulant that causes the relaxation of the smooth muscles through the increase of intracellular cyclic adenosine monophosphate (cAMP): bronchial and uterine muscles are relaxed, the peripheral vessels are dilated, heart rate increases and there are metabolic effects (eg. decrease of the plasma potassium levels)

MECHANISM OF ACTION



- Salbutamol binds and activates B2 receptor
- Activation of adenylyl cyclase
- Increased cyclic AMP levels
- Reduced intracellular calcium
- Smooth muscle relaxation

- Increased AMP levels

- Inhibit the release of inflammatory mediators from mast cells

- Reduced inflammation

ROUTES OF ADMINISTRATION

- Oral
- IV
- Subcutaneous
- Inhalation


Cipla
Salbutamol Inhalation IP
100 mcg/dose
asthalin
inhaler
dose counter


Salbutamol Tablets BP 4 mg
SAMOL-4


SALBUTAMOL INJECTION
YASHISAL
For IM / IV use
YASHICA

SIDE EFFECTS

- Taste alteration
- Shakiness in legs, arms, hands or feet
- Trembling or shaking of the hand or feet
- Fast, irregular, heartbeat or pulse
- Noisy breathing (rare)
- Redness of the skin (rare)

What is an expectorant?

- An expectorant is a type of cough medicine used to help clear mucus (phlegm) from your airway. You may take an expectorant to help relieve congestion if you have a cold or the flu. Expectorants are available as standalone drugs or as an ingredient in an all-in-one cold or flu medication.

Expectorant

- Expectorant also known as Mucokinetics , which those drugs are increase the movement of mucus . It promotes the secreation of sputum / mucus.
- They gives their action by increasing the bronchial secreation or by reducing the viscosity of mucus , which directly helps its removal by coughing .
- Expectorants that suppose to enhance the clearance of mucus.

Classification:

- **Bronchial secreation enhancers:**

sodium or potassium citrate, potassium iodide , guaiphenesin (glyceryl guaiacolate) , balsam of Tolu , vasaka, ammonium chloride.

- **Mucolytics:**

Bromhexine, Ambroxol , Acetyl cysteine , carbocisteine.

Mucus secreation enhancers

- Sodium and potassium citrate is increase bronchial secreation by salt action.
- Potassium iodide is secreted by bronchial glands and can irritate the airway mucosa. Prolonged use can affect thyroid function and produce iodism .
- Guaiphenesin, Tolu balsam , and vasaka are plant product that increase bronchial secreation and increase mucociliary clearance.
- Ammonium salts; Nauseating and reflexly increase bronchial secreation.

Guaiphenisin ; aids to clearing mucus from the airways improving breathing.

ADME :

Absorption; It is administered orally tablet or liquid form and Bioavailability is 50-60%.

Distribution:It does not have a highly extensive volume of distribution . It has low protein binding , it allows for rapid availability in systemic circulation.

Distribution .

Metabolism: It is primarily metabolized in liver to form inactive metabolites. To be processed by cytochrome P450 enzymes

Excretion: The metabolites and unchanged guaiphenesin primarily excreted via kidneys.the elimination of guaiphenesin is approximately 1 hours.

Mucolytics

- Mucolytics (derivatives of cysteine) reduce the disulfide bridges that bind glycoproteins to other protein such as Albumin and secretary IgA .
- This drug also act as antioxidant and may therefore reduce airflow inflammation .
- Various triggers like Oxidative stress, Cigarette smoke, inflammatory cytokines and activated TLRs stimulates the epdidermal growth factor Receptor (EGFR) which plays a critical role in airway mucus secreation from globlet cells and submucosal glands.
- Inhibitors of EGFR kinase such as gefinitib , and erlotinib are currently used for treatment of mucus hypersecreation.

Mucolytics

Bromhexine: alkaloid vasicine , obtained from adathoda vasaka . It is induce cupious bronchial secreation.

- Depolymerise the mucopolysaccharide and the tenacious sputum is broken when mucus plugs are present.
- Adverse effect: Rhinorrhea , lacrimation , gastric irritation, hypersensitivity.

Pharmacokinetics:

- Bromhexine is rapidly absorbed from the gastrointestinal tract and undergoes metabolism in the liver. Its oral bioavailability is stated to be only about 20%. It is widely distributed and plasma concentration reaches within 1-2 hours . About 85 to 90% of a dose is excreted in the urine mainly as metabolites.
- It has a terminal elimination half-life of up to about 12 hours. Bromhexine crosses the blood brain barrier and small amounts cross the placenta.

Mechanism of action

Mucus thinning; this is achieved by cleaving glycoprotein chains in the mucus which helps to reduce the thickness and making it less viscous.

Increased mucociliary clearance; By thinning the muscus , bromhexine facilitate the movement of cilia in the respiratory tract and enhancing the cleavage of mucus from the airways . This helps to improve breathing and reduce coughing .

Ambroxol; metabolites of bromhexine having similar mucolytics action . Dose 15 to 30 mg TDS

ADME :

Absorption; Bioavailability , Ambroxol is well absorbed after oral administration ,with a Bioavailability of approximately 70 %. It reaches peak plasma concentration

Within 1-3 hours .

- Distribution; Ambroxol has a large volume of distribution, it approximately 90% bound to plasma protein , which affect its distribution and half life.
- Metabolism; it is metabolized in the liver to various metabolites including glucuronides and dibromo derivatives .
- Excretion; the elimination of half life of ambroxol is around 8 hours.

90% of ambroxol and its metabolites are excreted via the kidney . Primarily as conjugated form with glucoronic acid

- Ambroxol may cause common side effects like nausea, vomiting, stomach discomfort, dry mouth, headache and dizziness etc

- Acetylcysteine;It opens the disulfide bonds in the mucoproteins present in sputum and makes it less viscous.
- It can be administered orally or inhalation as
- Adverse effect; orally administered acetylcysteine can rupture the gastric mucus (contraindicated in patient with peptic ulcer)

ADME:

- Absororption; Acetylcysteine has various oral Bioavailability ranging 6 to 10% due extensive first pass metabolism.peak plasma concentration reaches 1-2 hours.
- Distribution : it has low protein binding (approximately 50%) , which may influence it’s distribution in the body .
- Metabolism: Acetylcysteine metabolised in the liver through deacetylaton to cysteine.
- Excretion: The elimination half life is about 5.6 hours after intravenous administration and can vary after oral dosing. Approximately 90% of the dose is eliminated in urine.

Acknowledgement

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