Respiratory System (Antihistamines)

Histamine (HT) is a chemical messenger mostly generated and stored in granules of the mast cells as HT can be rapidly inactivated by the enzyme amine oxidase. HT, via multiple receptor systems, mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. It has no clinical applications, but agents that inhibit the action of HT have important therapeutic applications.

Most often, HT is just one of several chemical mediators released in response to stimuli. The stimuli for release of HT from tissues may include destruction of cells as a result of cold, toxins from organisms, venoms from insects and spiders, and trauma. Allergies and anaphylaxis can also trigger significant release of histamine.
Actions of HT are summarised in figure 1.

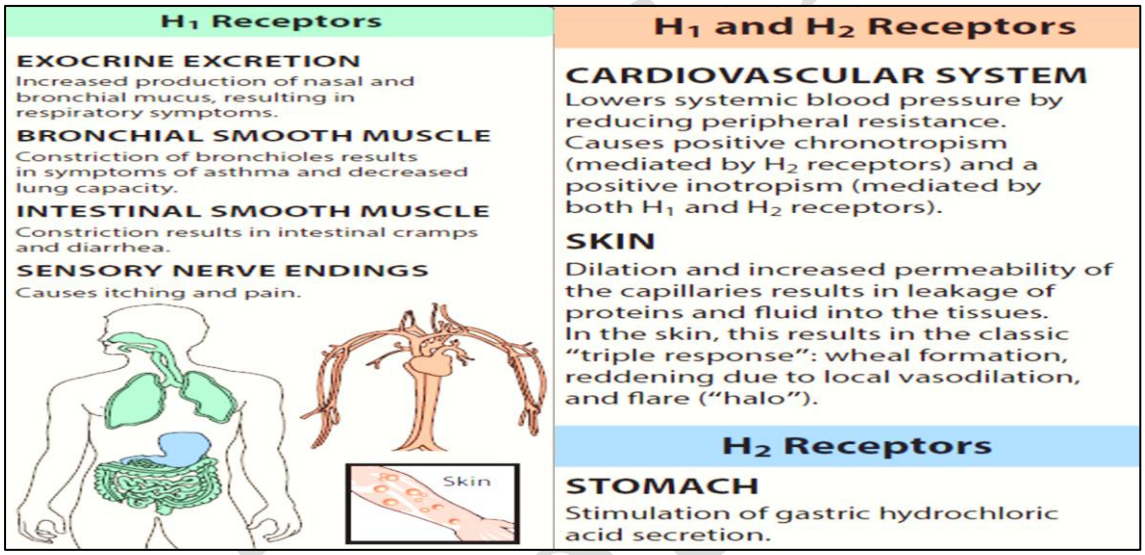

Figure1: Actions of histamine.

Role in allergy and anaphylaxis
The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include:
1- Contraction of airway smooth muscle
2- Stimulation of secretions
3- Dilation and increased permeability of the capillaries
4- And stimulation of sensory nerve endings.

Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include HT, serotonin, and leukotrienes. In some cases, these mediators cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response.
It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of HT is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction result. However, if HT release is too fast for efficient inactivation, a full-blown anaphylactic reaction occurs.

H1 ANTIHISTAMINES

- The term antihistamine refers primarily to the classic H1-receptor blockers. The H1-receptor blockers can be divided into 1st - and 2nd -generation drugs (Figure 2).
- The older 1st -generation drugs (FGDs) are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the CNS and cause sedation. FGDs tend to interact with other receptors, producing a variety of unwanted adverse effects.
- The 2nd-generation agents (SGAs) are specific for peripheral H1 receptors and do not penetrate the CNS because they are prepared as polar drugs. So, the SGAs do not penetrate the blood–brain barrier, causing less CNS depression than the FGDs.
- Among the SGAs, desloratadine, fexofenadine, and loratadine show the least sedation (Figure 2) as cetirizine and levocetirizine are partially sedating SGAs.

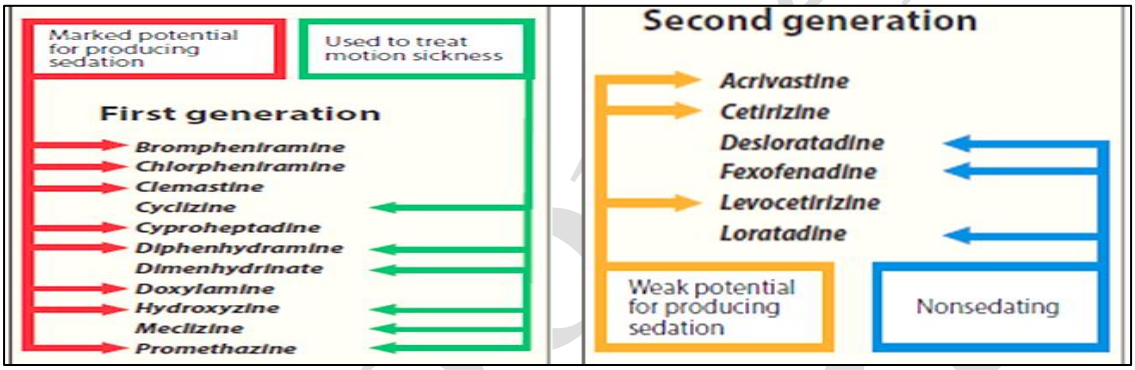

Figure 2: Summary of therapeutic advantages and disadvantages of some H1 histamine receptor–blocking agents.

Actions

- The action of all the H1-receptor blockers does not influence the formation or release of HT. Rather, they block the receptor-mediated response of a target tissue. They are much more effective in preventing symptoms than reversing them once they have occurred.
- H1-receptor antagonists can bind to cholinergic, adrenergic, or serotonin receptors as well.
- Antihistamines such as azelastine and ketotifen also have mast cell–stabilizing effects in addition to their HT receptor–blocking effects.

Therapeutic uses

1. Allergic and inflammatory conditions

- H1-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E (IgE) antibody for example:

a- Oral antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator released by mast cells.

b- Ophthalmic antihistamines, such as azelastine and ketotifen are useful for the treatment of allergic conjunctivitis.

c- The H1-receptor blockers are not indicated in treating bronchial asthma, because HT is only one of several mediators that are responsible for causing bronchial reactions.

- **Epinephrine** has actions on smooth muscle that are opposite to those of HT. Therefore, epinephrine is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.

2. Motion sickness and nausea:

a. Certain H1-receptor blockers, such as diphenhydramine, and promethazine are the most effective agents for prevention of the symptoms of motion sickness. They are usually not effective if symptoms are already present and, thus, should be taken prior to expected travel. The antiemetic action of these medications seems to be due to their blockade of central H1 and M1 muscarinic receptors.

3- Somnifacients: Although they are not the medications of choice, many FGDs such as diphenhydramine and doxylamine, have strong sedative properties and are used in the treatment of insomnia. These agents are available over-the-counter (OTC), or without a prescription. The use of FGDs H1 antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical. The SGAs of antihistamines have no value as somnifacients.

Pharmacokinetics

H1-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average plasma half-life is 4 to 6 hours, except for that of meclizine and the SGAs, which is 12 to 24 hours allowing once-daily dosing.

Adverse effects

The side effects of the antihistamine drugs vary according to the affinity of the drug to the receptors and the drug's structure. So, some side effects may be undesirable, and others may be of therapeutic value.

First-generation H1 antihistamines, such as chlorpheniramine and diphenhydramine, bind to H1 receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation. Diphenhydramine may cause paradoxical hyperactivity in young children. Other central actions include fatigue, dizziness, lack of coordination, and tremors. Sedation is less common with the SGAs, since they do not readily enter the CNS. Second-generation H1 antihistamines are specific for peripheral H1 receptors.

Other effects: First-generation antihistamines exert anticholinergic effects, leading not only to dryness in the nasal passage but also to a tendency to dry out the oral cavity. They also may cause blurred vision and retention of urine. The most common adverse reaction associated with SGAs is headache.

Drug interactions:

Interaction of H1-receptor blockers with other drugs can cause serious consequences, such as potentiation of effects of other CNS depressants, including alcohol.

Overdoses: Although the margin of safety of H1-receptor blockers is relatively high, and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the

CNS, including hallucinations, excitement and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.

HISTAMINE H2-RECEPTOR BLOCKERS

Histamine H2-receptor blockers (such as cimetidine and ranitidine) have little, if any, affinity for H1 receptors. Although antagonists of the histamine H2 receptor (H2 antagonists or H2-receptor blockers) block the actions of HT at all H2 receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn.

Drugs for Disorders of Respiratory System

Asthma, chronic obstructive pulmonary disease (COPD), and allergic rhinitis are commonly encountered respiratory disorders. Each of these conditions may be associated with a troublesome cough, which may be the only presenting complaint.

Drugs used to treat respiratory conditions can be delivered topically to the nasal mucosa, inhaled into the lungs, or given orally or parenterally for systemic absorption. Local delivery methods, such as nasal sprays or inhalers, are preferred to target affected tissues while minimizing systemic side effects.

Asthma

Asthma is a chronic inflammatory disease of the airways characterized by episodes of acute airflow obstruction, which is due to bronchoconstriction that results from contraction of bronchial smooth muscle, inflammation of the bronchial wall, and increased secretion of mucus. The underlying inflammation of the airways contributes to airway hyperresponsiveness, airflow limitation, respiratory symptoms, and disease chronicity. Asthma attacks may be triggered by exposure to allergens, exercise, stress, and respiratory infections leading to shortness of breath, cough, chest tightness, wheezing, and rapid respiration.

Goals of therapy

The goals of asthma therapy are to decrease the intensity and frequency of asthma symptoms and the degree to which the patient is limited by these symptoms.
All patients need to have a "quick-relief" medication to treat acute asthma symptoms while drug therapy for long-term control of asthma is designed to reverse and prevent airway inflammation.

Preferred drugs used to treat asthma

1- β2-Adrenergic agonists

Inhaled β2-adrenergic agonists directly relax airway smooth muscle. They are used for the quick relief of asthma symptoms, as well as adjunctive therapy for long-term control of the disease.

Quick relief drugs

- Short-acting β2 agonists (SABAs) have a rapid onset of action (5 to 30 minutes) and provide relief for 4 to 6 hours. They are used for symptomatic treatment of

bronchospasm, providing quick relief of acute bronchoconstriction. So, all patients with asthma should be prescribed a SABA inhaler.

- β2 agonists have no anti-inflammatory effects, and they should never be used as the sole therapeutic agents for patients with persistent asthma. However, monotherapy with SABAs may be appropriate for patients with intermittent asthma or exercise-induced bronchospasm.
- Direct acting β2-selective agonists (include albuterol and levalbuterol) can provide significant bronchodilation with little of the undesired effect of α or β1 stimulation.
- Adverse effects, such as tachycardia, hyperglycemia, hypokalemia, and hypomagnesemia, are minimized with inhaled delivery versus systemic administration. These agents can cause β2-mediated skeletal muscle tremors.

Long-term control drugs:

- Salmeterol and formoterol are long-acting β2 agonists (LABAs). They have a long duration of action, providing bronchodilation for at least 12 hours. Neither salmeterol nor formoterol should be used for quick relief of an acute asthma attack. LABAs should be used only in combination with an asthma controller medication.
- Inhaled corticosteroids (ICS) remain the long-term controllers of choice in asthma, and LABAs are considered to be useful adjunctive therapy for attaining asthma control. Adverse effects of LABAs are similar to quick-relief β2 agonists.

2- Corticosteroids (CS)

ICS are the drugs of choice for long-term control in patients with any degree of persistent asthma. CS inhibit the release of arachidonic acid, thereby producing direct anti-inflammatory properties in the airways. No other medications are as effective as ICS in the long-term control of asthma in children and adults.
To be effective in controlling inflammation, glucocorticoids must be used regularly. Severe persistent asthma may require the addition of a short course of oral glucocorticoid treatment.

Actions on lung: ICS do not directly affect the airway smooth muscle. Instead, ICS therapy directly targets underlying airway inflammation by decreasing the inflammatory cascade, reversing mucosal edema, decreasing the permeability of capillaries, and inhibiting the release of leukotrienes.
After several months of regular use, ICS reduce the hyperresponsiveness of the airway smooth muscle to a variety of bronchoconstrictor stimuli, such as allergens, irritants, cold air, and exercise.

Routes of administration

a. **Inhalation:** The development of ICS has markedly reduced the need for systemic CS treatment to achieve asthma control. However, as with all inhaled medications, appropriate inhalation technique is critical to the success of therapy.

Inhaler technique

Appropriate inhaler technique differs between metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), so assessing technique regularly is critical to the success of therapy.

Metered-dose inhalers and dry powder inhalers

- MDIs have propellants that eject the active medication from the canister. Patients should be instructed to inhale **slowly** and **deeply** just before and throughout actuation of the inhaler to avoid impaction of the medication onto the laryngeal mucosa, rather than the bronchial smooth muscle.
- A large fraction (typically 80% to 90%) of inhaled glucocorticoids is either deposited in the mouth and pharynx or swallowed while the remaining (10% to 20% of the dose) is deposited in the airway.
- If ICS are inappropriately inhaled, systemic absorption and adverse effects are much more likely.
- DPIs require a different inhaler technique. Patients should be instructed to inhale **quickly** and **deeply** to optimize drug delivery to the lungs.

b. Oral/systemic: Patients with a severe exacerbation of asthma (status asthmaticus) may require intravenous methylprednisolone or oral prednisone to reduce airway inflammation. In most cases, suppression of the hypothalamic–pituitary–adrenal cortex axis will not occur during the short course of oral prednisone "burst" typically prescribed for an asthma exacerbation. Therefore, prednisone dose taper is unnecessary prior to discontinuation.

Adverse effects: Oral or parenteral glucocorticoids have a variety of potentially serious side effects, whereas ICS, particularly if used with a spacer, have few systemic effects. ICS deposition on the oral and laryngeal mucosa can cause adverse effects, such as oropharyngeal candidiasis (due to local immune suppression) and hoarseness. Patients should be instructed to rinse the mouth in a "swish-and-spit" method with water following use of the inhaler to decrease the chance of these adverse events.

Alternative drugs used to treat asthma

These drugs are useful for treatment of asthma in patients who are poorly controlled by conventional therapy or experience adverse effects secondary to CS treatment. These drugs should be used in conjunction with ICS therapy for most patients, not as monotherapy.

A. Leukotriene modifiers

- Leukotrienes (LT) B4 and the cysteinyl LT, are important materials in the inflammatory cascade as LTB4 is a potent chemoattractant for neutrophils and eosinophils, whereas the cysteinyl leukotrienes constrict bronchiolar smooth muscle, increase endothelial permeability, and promote mucus secretion.
- Zileuton is a selective and specific inhibitor of 5-lipoxygenase, preventing the formation of both LTB4 and the cysteinyl leukotrienes.
- Because zafirlukast and montelukast are selective antagonists of the cysteinyl leukotriene-1 receptor, they block the effects of cysteinyl leukotrienes. All three drugs are approved for the prevention of asthma symptoms.
- They should not be used in situations where immediate bronchodilation is required. Leukotriene receptor antagonists have also shown efficacy for the prevention of exercise induced bronchospasm.
- All three drugs are orally active and highly protein bound.

- **Adverse effects:** elevations in serum hepatic enzymes have occurred with all three agents, requiring periodic monitoring and discontinuation when enzymes exceed three to five times the upper limit of normal.

B. Cromolyn

- Cromolyn is a prophylactic anti-inflammatory agent that inhibits mast cell degranulation and release of HT. It is an alternative therapy for mild persistent asthma. However, it is not useful in managing an acute asthma attack, because it is not a bronchodilator. It is available as a nebulized solution for use in asthma.
- Due to its short duration of action, this agent requires dosing three or four times daily, which affects adherence and limits its use. Adverse effects are minor and include cough, irritation, and unpleasant taste.

C. Cholinergic antagonists

- The anticholinergic agents block vagally mediated contraction of airway smooth muscle and mucus secretion.
- Inhaled ipratropium, a quaternary derivative of atropine, is not recommended for the routine treatment of acute bronchospasm in asthma, as its onset is much slower than inhaled SABAs. However, it may be useful in patients who are unable to tolerate a SABA or patients with concomitant COPD.
- Ipratropium also offers additional benefit when used with a SABA for the treatment of acute asthma exacerbations in the emergency department.
- Adverse effects such as xerostomia and bitter taste are related to local anticholinergic effects.

D. Theophylline

- Theophylline is a bronchodilator that relieves airflow obstruction in chronic asthma and decreases its symptoms. It may also possess anti-inflammatory activity, although the mechanism of action is unclear.
- Previously, the mainstay of asthma therapy, theophylline has been largely replaced with β2 agonists and corticosteroids due to its narrow therapeutic window, adverse effect profile, and potential for drug interactions.
- Overdose may cause seizures or potentially fatal arrhythmias.
- Serum concentration monitoring should be performed when theophylline is used chronically.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.
2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.