Pharmacology Summarization

Done by: Mohammad Abuassi

CHAPTER 30
Antihistamines

1. Location: Histamine is present in practically all tissues, with significant amounts in the lungs, skin, blood vessels, and GI tract. It is found at high concentration in mast cells and basophils. Histamine functions as a neurotransmitter in the brain. It also occurs as a component of venoms and in secretions from insect stings.

2. Synthesis: Histamine is an amine formed by the decarboxylation of the amino acid histidine by the enzyme histidine decarboxylase, which is expressed in cells throughout the body, including neurons, gastric parietal cells, mast cells, and basophils. In mast cells, histamine is stored in granules. If histamine is not stored, it is rapidly inactivated by the enzyme amine oxidase.

3. Release of histamine: Most often, histamine is just one of several chemical mediators released in response to stimuli. The stimuli for release of histamine 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.

*Histamine released in response to certain stimuli exerts its effects by binding to various types of histamine receptors (H1, H2, H3, and H4).
*Histamine is the main cause of allergy or anaphylactic shock.
*Symptoms associated with allergy and anaphylactic shock include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings.

II. H1 ANTIHISTAMINES

The term antihistamine refers primarily to the classic H1-receptor blockers. The H1-receptor blockers can be divided into first- and second generation Drugs. However, most of these drugs penetrate the CNS and cause sedation.

* Most of these compounds do not influence the formation or release of histamine. Rather, they block the receptor-mediated response of a target tissue. They are much more effective in preventing symptoms.
* However, most of these agents have additional effects unrelated to their ability to block H1 receptors. These effects reflect binding of the H1-receptor antagonists to cholinergic, adrenergic, or serotonin receptors.
* Allergic and inflammatory conditions: H1-receptor blockers are useful in treating and preventing allergic reactions caused by antigens acting on immunoglobulin E antibody, the H1-receptor blockers are not indicated in treating bronchial asthma, because histamine is only one of several mediators that are responsible for causing bronchial reaction.

[Note: Epinephrine has actions on smooth muscle that are opposite to those of histamine. It acts via β receptors on smooth muscle, causing cAMP-mediated relaxation. Therefore, epinephrine is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.]

*Motion sickness and nausea:** 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 antihistamines prevent or diminish nausea and vomiting mediated by both the chemoreceptor and vestibular pathways.

*Somnifacients:** These agents are available over-the-counter (OTC), or without a prescription. The use of first-generation H1 antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical. The second-generation antihistamines have no value as somnifacients.

C. 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 second-generation agents, which is 12 to 24 hours.

Adverse effects

First-generation H1-receptor blockers have a low specificity, interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors.
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1. Sedation: First-generation H₁ antihistamines, such as chlorpheniramine [klor-phen-IR-a-meen], diphenhydramine, hydroxyzine [hye-DROX-ee-zeen], and promethazine, bind to H₁ receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation (Figure 30.7). 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 second-generation drugs, since they do not readily enter the CNS. Second-generation H₁ antihistamines are specific for peripheral H₁ receptors.

2. 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 second-generation antihistamines is headache. Topical formulations of diphenhydramine can cause hypersensitivity reactions such as contact dermatitis when applied to the skin.

3. 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. Patients taking monoamine oxidase inhibitors (MAOIs) should not take antihistamines because the MAOIs can exacerbate the anticholinergic effects of the antihistamines. In addition, the first-generation antihistamines (diphenhydramine and others) with anticholinergic (antimuscarinic) actions may decrease the effectiveness of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in the treatment of Alzheimer’s disease.

4. 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, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system.