Lecture 1: Antihistamines

Drugs that block histamine's actions

Histamine is an endogenous locally acting substance present in various tissues of the body, also called "Autacoid" (Greek "self-remedy") or local hormone because it acts locally at the site of release.

- Present mainly in the skin, lung and gastrointestinal tissues, as these tissues are in direct contact to the outside of the body. It's also stored near blood vessels and in the CNS.
- Histamine is usually released with other chemical mediators of inflammation).
- **Histamine** is a small molecule **synthesized** and **stored** in 2 types of cells, **mast cells** and **basophils** and stored in **structures** called **secretory granules**. In the **CNS**, histamine produced by **neurons**. In the **Gastric mucosa**, stimulate **gastric acid** secretion by **parietal cells**.
- Release of histamine is produced by allergic and non allergic mechanisms.
- Histamine has great interest because of its role in pathologic (disease) states: **Allergic disorders** or reactions and **Peptic ulcer** disease

Physiologic and Pharmacologic Effects

- Histamine acts primarily through two types of receptors, named **H_1, and H_2 receptors.** The response produced depends on which of these receptors is involved

- **Stimulation of H_1 receptors** → the responses include:

1. Vasodilation: dilation of small blood vessels especially in the skin of the face and upper body causing the area to become warm and flushed.
2. Increased capillary permeability → escape of fluid, protein and platelet into the interstitial space produces edema.
3. Bronchoconstriction: constriction of bronchi.
4. CNS effects → H_1 receptors have role in cognition, memory, and the cycle of sleeping and waking.
5. Activation of H_1 receptors on the sensory nerve produces itching and pain.
6. Activation of H_1 receptors also promotes secretion of mucus.

- **Stimulation of H_2 receptors** → the major response is secretion of gastric acid. Histamine is the dominant regulator of gastric acidity; it acts directly on parietal cells of the stomach to promote acid release.

- **✶ Despite impressive variety of actions, clinical application for histamine itself are limited, currently is restricted to diagnostic procedures.**

- **Antihistamines:** a widely used family of drugs, and fall into **2 basic categories:**

1. H_1 antagonists or blockers – Classic antihistamines – produce selective blockade of H_1 receptor – used to treat mild allergic disorders, and also classified into

1) First-generation H_1 antagonists – Highly sedative

2) Second-generation H_1 antagonists – Non-sedative

- All of the H1 blockers can be administered by mouth. In addition, some can be given parenterally, by nasal spray, or by rectal suppository.

2. H_2 antagonists or blockers – produce selective blockade of H_2 receptor – used to treat gastric and duodenal ulcers.

Examples

First-generation H_1 antagonists

Drugs and Routes	Usual adult dosage
Diphenhydramine – (Allermine) -- PO, IV, IM	25-50 mg 2–3 times daily
Chlorpheniramine (Histadin) -- PO	4 mg 4 -6 hrs
Dexchlorpheniramine (Polaramine) -- PO	2 mg 4-6 hrs
Promethazine -- PO, IV, IM, Rectal supp.	10–20 mg 2–3 times daily
Ketotifen -- PO	1 mg twice daily
Cyproheptadine (Periactin) -- PO	4 mg 3–4 times daily
Cinnarizine (Stugeron) -- PO	30 mg 2 hrs before travel then15 mg every 8 hours
Triprolidine --PO Triprolidine/pseudoephedrine (Actifed) -- PO	2.5 mg 4-6 hrs 2.5 mg/60 mg 4-6hrs
Clemastine (Tavegil) -- PO	1 mg twice daily

Second-generation H_1 antagonists

- Second-generation antihistamines exert little or no sedative effect than first-generation agents

Drugs	Routes	Usual adult dosage
Acrivastine	PO	8 mg 3 times daily
Loratadine Desloratadine	PO	10 mg once daily 5 mg once daily
Cetirizine Levocetirizine (is an isomer of cetirizine)	PO	10 mg once daily 5 mg once daily
Fexofenadine	PO	120/180 mg once daily
Azelastine	Nasal Spray	
Mizolastine	PO	10 mg once daily

Mechanism of Action of antihistamine:

- H_1 antagonists are structurally related to histamine and bind selectively to $Histamine_1$ receptors thereby blocking or preventing the actions of histamine from acting on target tissues.
- They do not prevent histamine release or reduce the amount released.
- Antihistamines block most of, but not all, the effects of histamine.
- Antihistamines can also bind to non-histamine receptors – the ability of certain antihistamines to bind & block muscarinic receptors (atropine-like) – blockade of these receptors underlies several important side effects.
- H_1 antagonists have no effect at H_2 receptors.

Pharmacologic effects of antihistamines

✧Peripheral effects

- In small bl. Vessels of the skin – inhibit the dilator actions of histamine, & thereby reduce localized flushing.
- In capillary beds – prevent histamine-induced increases capillary permeability and thereby reduce edema.
- By blocking histamine at sensory nerve, H_1 antagonists reduce itching & pain.
- Blockade of H_1 receptors in mucous membranes – suppresses secretion of mucous.

✧**Effects on CNS** – antihistamines can cause both depression & excitation of the CNS.

- At therapeutic doses usually produce depression of the CNS (drowsiness, diminish alertness, slow reaction).
- Overdose can produce CNS stimulation or excitation (convulsion esp. in children).

✧ **Other effects*:*** Blockade of muscarinic cholinergic receptors – can produce typical anticholinergic responses.

Therapeutic uses: Antihistamines are used for a variety of allergic and non-allergic disorders.

1. Relief symptoms of mild allergic conditions such as seasonal allergic rhinitis, acute urticaria, and urticaria associated with mild transfusion reactions (benefits result from H1receptor blockade)

2. Adjunctive therapy in treatment of Anaphylactic reactions – Epinephrine is the drug of choice for treating severe anaphylaxis or severe allergy because antihistamines do not effective in treating bronchoconstriction and hypotension.

Antihistamines are not useful in bronchial asthma due to the anticholinergic effects.

3. Common cold: Antihistamines are common ingredients in OTC cold remedies. Despite their widespread presence in cold remedies, antihistamines are of practically no value against the common cold. These drugs neither prevent colds nor shorten their duration. The only benefit that these drugs may offer is a moderate reduction in rhinorrhea and sneezing (an effect that derives from their anticholinergic properties).

4. Miscellaneous uses for non-allergic disorders, such as

- Relief of nausea and vomiting, and motion sickness, benefits derive from blockade of H_1 receptors and muscarinic receptors (cinnarizine, cyclizine, and promethazine).
- Insomnia – used for sedation or sleep: antihistamines can induce sleep when used in sufficient dosage, this can be useful in the treatment of anxiety associated with allergic diseases. (e.g., diphenhydramine).
- Adjuncts to analgesics

Adverse effects and nursing interventions

- **Adverse effects** mainly associated with **first-generation H_1 antagonists.**
- These responses are more of a nuisance than a source of serious discomfort or danger. Frequently, side effects subsides with continued use.
- **Sedation** – the most common side effect of the antihistamines, and can lead to serious consequences. For students, sedation can impair learning and memory. For drivers, sedation greatly increases the risk of an accident.

✓**Accordingly, patients should exercise extreme caution when driving or doing other hazardous activities. If a preparation with a long half-life is being used, daytime sedation can be minimized by administering the entire daily at night.**

- **Non-sedative CNS effects:**
- In addition to sedation, antihistamines can cause dizziness, incoordination, confusional states, and fatigue. Older patients are especially sensitive to these actions.
- In some patients, CNS stimulation or excitation occurs, resulting in insomnia, nervousness, tremors, and even convulsions. CNS stimulation is most common in children and following overdose.

✓**Accordingly, exercise caution when treating young children and older adults**

- **GI effects or disturbance** (nausea, vomiting, loss of appetite, diarrhea, constipation) are common.

✓**These reactions can be minimized by administering antihistamines with food.**

- **<u>Anti-cholinergic effects</u>:** H_1-histamine antagonists have weak anti-cholinergic effects. These responses can produce drying of mouth and throat, blurring of vision, retention of urine.

✓**Advise patients that dryness of the mouth and throat can be reduced by using hard sugarless candy and taking frequent sips of liquid.**

- Antihistamines should be used with caution in patients with asthma, because thickening of bronchial secretions may impair breathing.
- Other anti-cholinergic effects (urinary hesitancy, tachycardia, constipation) are not usually problems.
- **<u>Severe local tissue injury</u>**. Extravasation of IV promethazine can cause severe local tissue injury, including gangrene that requires amputation. Accordingly, when parenteral dosing is needed, the preferred route is IM.

✓**Advise patients to immediately report local burning or pain.**

- ☆Second-generation antihistamines are the non-sedative and less CNS effects because
- (1) the second-generation agents cross the blood-brain barrier poorly and
- (2) they have a low affinity for H1 receptors of the CNS.

- ☆The second-generation antihistamines are the least anticholinergic adverse effects.

- **Contraindications to Use – High-risk pts:**

x Patients with hypersensitivity to the drugs

x The margin of safety of antihistamines in pregnancy is unknown – used only when clearly necessary& when the benefits of treatment outweigh the potential risks to the fetus.

✓ Antihistamines should be avoided late in the 3rd trimester, since newborns are practically sensitive to the adverse actions of these drugs.

x Antihistamines should be avoided in nursing mothers and newborn infants.

x Exercise caution when treating young children, older adults, and patients with conditions that may be aggravated by muscarinic blockade, including asthma, urinary retention, glaucoma, hypertension, and prostatic hypertrophy.