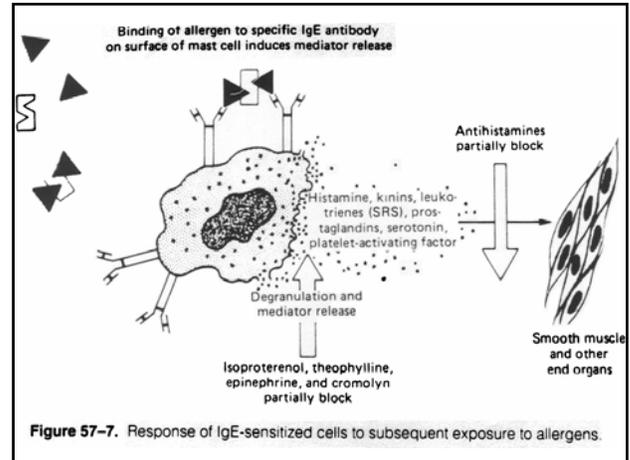


Conditions That Release Histamine

1. Tissue injury: Any physical or chemical agent that injures tissue, skin or mucosa are particularly sensitive to injury and will cause the immediate release of histamine from mast cells.
2. Allergic reactions: exposure of an antigen to a previously sensitized (exposed) subject can immediately trigger allergic reactions. If sensitized by IgE antibodies attached to their surface membranes will degranulate when exposed to the appropriate antigen and release histamine, ATP and other mediators.
3. Drugs and other foreign compounds: morphine, dextran, antimalarial drugs, dyes, antibiotic bases, alkaloids, amides, quaternary ammonium compounds, enzymes (phospholipase C). Penicillins, Tetracyclines, Basic drugs- amides, amidines, diamidines, Toxins, venoms, Proteolytic enzymes, Bradykinin, Kallidin, & Substance P



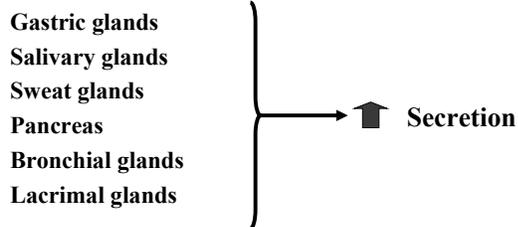
3 Types of Histamine Receptors

1. H₁ receptors: mediate effects on smooth muscle leading to vasodilation, increased vascular permeability, and contraction of nonvascular smooth muscle.
2. H₂ receptors: mediate histamine stimulation of gastric acid secretion and may be involved in cardiac stimulation.
3. H₃ receptors: feedback inhibitors in CNS, gastrointestinal tract, lung, heart.

Pharmacological Effects of Histamine

1. Cardiovascular system.
 - a) triple effect on terminal vasculature (itching & pain):
 - i. reddening at injection site due to vasodilation
 - ii. wheal or disk of edema within 1 to 2 min
 - iii. a large, bright crimson flare or halo surrounding the wheal
 - b) i.v. histamine: fall in blood pressure, cutaneous flushing, over the face and upper trunk, rise in skin temperature, intense headache.
2. Smooth muscle of bronchioles; causes contraction of nonvascular smooth muscle. Asthmatics may experience marked bronchial constriction compared with normal subjects.
3. Exocrine glands: potent stimulator of gastric secretion (HCl & pepsin), enhances salivary and lacrimal gland secretion (minimal unless large doses are given), stimulates chromaffin cells in adrenal medulla to secrete catecholamines.
4. Peripheral Nervous system: itching and pain

Pharmacological Effects: Exocrine Glands



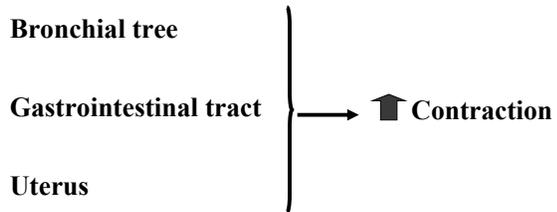
Pharmacological Effects: Arterioles, Capillaries & Venules

Vasodilation

Increased permeability, (edema)

Systemic hypotension

Pharmacological Effects Effects: Vascular Smooth Muscles



Antihistamines Background

Daniel Bovet, Nobel Prize 1944

Synthesized first antihistamines

Compounds appeared to prevent the binding of histamine to H_1 receptors through their structural similarities

General Mechanism of Action of Antihistamines

Blocks action of histamine at receptor

Competes with histamine for binding

Displaces histamine from receptor

Most beneficial when given early

Histamine vs. Antihistamine Cardiovascular Effects

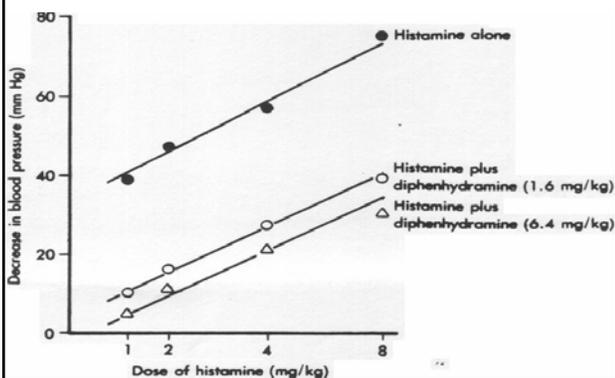
Histamine

dilation of small blood vessels / increased permeability

Antihistamine

prevents dilation / prevents increased permeability

Histamine Decreases Blood Pressure



Histamine vs. Antihistamine: Smooth Muscle Effects

Histamine

Stimulates exocrine glands (salivary, gastric, lacrimal, & bronchial secretions)

Antihistamine

prevents: salivary, gastric, lacrimal, & bronchial secretions

Histamine vs. Antihistamine: Immune Effects

Histamine

mast cell release: histamine & other substances released

Antihistamine

bind to receptors and prevents histamine from eliciting a response

Diagnostic Uses of Histamine

1. Sampling gastric acid content, 1 mg histamine subcutaneously to stimulate gastric secretion (no major effects on blood vessels).
2. Pulmonary function (for diagnosing asthma).
3. Sensory nerve function.

Therapeutic Uses of H₁ Blockers

1. Allergic rhinitis, relieves rhinorrhea, sneezing, and itching of eyes and nasal mucosa.
2. Common cold: palliative, dries out the nasal mucosa. Often combined with nasal decongestant and analgesics.
3. Allergic dermatoses: can control itching associated with insect bites.
4. Outpatient procedures for preanesthetic sedation and prevention of nausea and vomiting (Promethazine (Phenergan)). Phenergan also inhibits salivary and bronchial secretions and can be used as a local anesthetic.
5. Antiemetic: prevention or treatment of nausea and vomiting (Bendectin, doxylamine with pyridoxine).
6. Hypnotics: limited value.
7. Other uses:
 - a. Reduction of tremors and muscle rigidity in Parkinson's disease
 - b. Treatment of migraine headaches

Actions Not Caused by H₁ Receptor Blockade

1. antinausea and antiemetic effects (antimuscarinic effects)
2. antiparkinsonism effects (antimuscarinic effects)
3. peripheral antimuscarinic effects
4. adrenoceptor-blocking actions (phenothiazines)
5. manifested as orthostatic hypotension
6. serotonin-blocking action (cyproheptadine)
7. local anesthesia, blockade of sodium channels (diphenhydramine and promethazine)

Mechanism of Action: H₁ Antagonists

Displaces histamine from the H₁ receptor, which is a G-protein coupled receptor

Histamine leads to formation of IP₃ and a release of stored Ca⁺⁺, followed by a cascade of other events.

H₁ receptor blockade prevents this activity and leads to a decrease in Ca⁺⁺ inside of the cell

Toxic Reactions & Side Effects of H₁ Blockers

1. CNS depression (mainly in first generation agents).
2. Allergic reactions (topical application).
3. Appetite loss, nausea and vomiting, constipation or diarrhea.
4. Insomnia, tremors, nervousness, irritability, tachycardia, dry mouth, blurred vision, urinary retention, constipation (1st generation).
5. CNS stimulation with hallucinations, motor disturbances (tremors and convulsions), and death.
6. Secreted in breast milk and can cross the placenta.

Drug Interactions of H₁ Blockers

1. Antihistamines that produce sedation can potentiate CNS depressants (e.g., barbiturates, opiates, general anesthetics, and alcohol)
2. Antihistamines that possess anticholinergic actions can produce manifestations of excessive blockade if given with anticholinergic drugs (e.g., dry mouth, constipation, or blurred vision)
3. Terfenadine (Seldane) taken with grapefruit juice or erythromycin or other drugs that inhibit the enzyme, CYP3A4 can lead to cardiac toxicity. Taken off the market.

First Generation Antihistamines

Side Effects

Sedating

Anticholinergic

Many available Over-the-Counter (OTC)

Inexpensive (Average \$4.50/pack)

56% of allergy sufferers use OTC, but only \$325 million in sales

First Generation Antihistamines

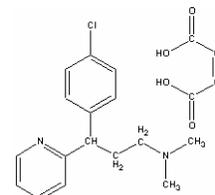
1. Alkylamines
2. Ethanolamines
3. Ethylenediamines
4. Piperazines
5. Phenothiazines
6. Piperadines

First Generation Antihistamines (Alkylamines)

Chlorpheniramine maleate
(Chlor Trimeton®)

Schering (1949)

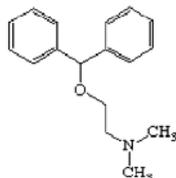
Currently sold OTC by
Schering-Plough
Healthcare Products



First Generation Antihistamines (Ethanolamines)

Diphenhydramine HCl (Benadryl®)
Parke Davis (1946)

Currently sold OTC by Pfizer,
Inc., Warner-Lambert
Consumer Healthcare

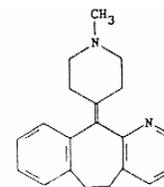


First Generation Antihistamines (Piperadines)

Azatadine (Optimine®)

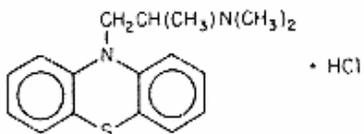
Schering (1977)

Available only by
prescription



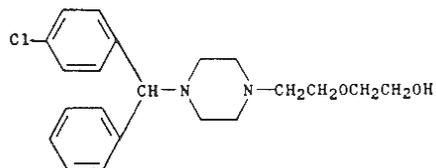
First Generation Antihistamines (Phenothiazines)

Promethazine HCl (Phenergan®)
Wyeth (1951)
Available only by prescription



First Generation Antihistamines (Piperazines)

Hydroxyzine HCl (Atarax®)
Pfizer (1956)
Available only by prescription

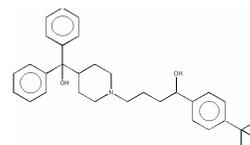


Second Generation Antihistamines

Generally do not cause the sedation and drying seen in first generation antihistamines
Do not cross the blood-brain barrier as readily as First Generation compounds
Lipophobicity
Large molecular size
Electrostatic charge

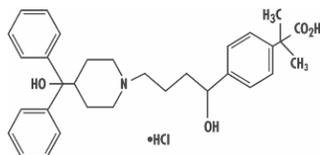
Second Generation Antihistamines: Terfenadine (Seldane®)

Non-sedating
Caused fatal heartbeat irregularities when taken with certain drugs and foods
Ketoconazole, erythromycin, grapefruit juice interfered with drug metabolism increasing the concentration of terfenadine in bloodstream
Removed from the market (1992)



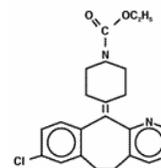
Second Generation Antihistamines: Fexofenadine HCl (Allegra®)

Safe metabolite of Terfenadine
FDA approved on July 25, 1996
Non-sedating (FAA, Air force, Navy approved)
Clinical studies showed no cardiac side effects



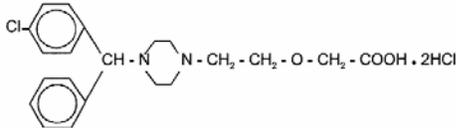
Second Generation Antihistamines: Loratadine (Claritin®)

Schering-Plough, Inc. FDA approved 1993
Developed from Azatadine
Non-sedating (FAA, Air force, Navy approved)
No reported cardiac side effects up to 160 mg

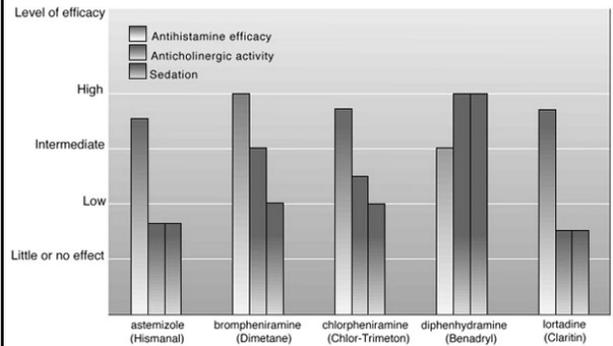


Second Generation Antihistamines: Cetirizine (Zyrtec®)

Pfizer, Inc and UCB Pharma Inc.
 FDA approved 1995
 Metabolite of hydroxyzine
 Effective against rash/hives
 No reported cardiac side effects
 Potential for sedation



Specificity of Selected H₁ Blockers



OTC Available H₂ Antagonists

1. cimetidine (Tagamet) associated with most side effects
2. ranitidine (Zantac)
3. famotidine (Pepcid)
4. nizatidine (Axid)

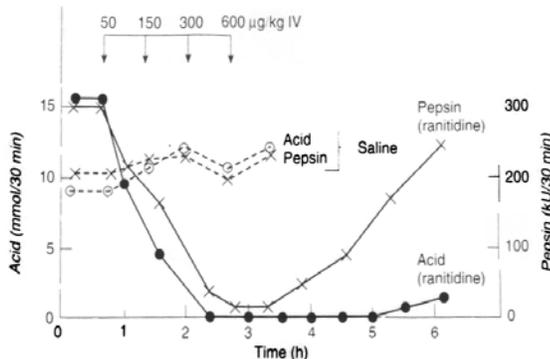
H₂ Antagonist Pharmacological Effects

1. Competitive antagonists at the H₂ receptors
2. Inhibits secretory function of gastric mucosa.
3. Few other effects than those on gastric secretion.
4. Reduces gastric acid volume & concentration of pepsin

Most Common Adverse Effects

1. Diarrhea
2. Dizziness
3. Somnolence
4. Headache
5. Rash
6. Constipation
7. Vomiting
8. Arthralgia

H₂ Blockers Decrease Gastric Acid Release



H₂ Antagonist Therapeutic Uses

1. Duodenal ulcer
2. Gastric ulcer
3. Zollinger-Ellison syndrome (a pathological hypersecretory state resulting in excessive gastric pepsin & HCl)
4. Gastroesophageal reflux disease
5. Used prior to surgery in patients with GI obstruction to elevate gastric pH
6. Reflux esophagitis
7. Antacid

H₂ Antagonists: Mechanisms of Action

Displaces histamine from the H₂ receptor, a G-protein coupled receptor

Because histamine activates cAMP, H₂ blockers lead to a decrease in cAMP and a concomitant decrease in Ca⁺⁺

Toxic Reactions (Mostly Associated With Cimetidine (Tagamet))

1. Most common (seen in only 1-2% of patients): diarrhea, dizziness, somnolence, headache, and rash. Also constipation, vomiting and arthralgia.
2. CNS effects: slurred speech, delirium, confusion. Most commonly seen in older patients or those with liver or kidney impairment
3. Endocrine function (minor and reversible): antiandrogen effects, e.g., loss of libido, impotence, reduced sperm count
4. Blood dyscrasias.
5. Liver: reversible cholestasis.

H₂ Antagonist Drug Interaction

Cimetidine: increased activity of drugs that are metabolized through cytochrome P450 pathway and also reduces blood flow through the liver including. e.g., warfarin, phenytoin, propranolol, metoprolol, quinidine, caffeine, lidocaine, theophylline, benzodiazepines, ethanol, tricyclic antidepressants, and calcium channel blockers.

All H₂ blockers except famotidine (Pepcid) increase the bioavailability of ethanol.

Agents that inhibit gastric secretion alter the bioavailability and rate of absorption of many other drugs

H₃ Receptor Drugs

Believed to act as feedback inhibitors in a wide variety of organ systems in the CNS, agonists cause sedation

GI: agonists down regulate histamine. Thereby decreasing gastrin

Lung: agonists have a bronchodilatory effect

Clinical Uses

None (Drugs are available only for research purposes)

Mechanisms of Action

G-protein coupled receptor, decreases of intracellular Ca⁺⁺

Inhibitors of Histamine Release

Cromolyn sodium (Intal, Nasalcrom)
Nedocromil Sodium

in vitro studies : Reduces the release of histamine, other granular contents & leukotriene production.

Devoid of bronchodilating capability

Inhibits pulmonary mast cell degranulation in response to a variety of stimuli including the interaction between cell-bound IgE and specific antigen.

Does not relax bronchial or other smooth muscle *in vitro* or, in the short term, *in vivo*. However, long term administration diminishes bronchial hyperactivity.

Histamine Release Inhibitors: Therapeutic Uses

mild to moderate bronchial asthma to prevent asthma attacks.

effective in children

reduces need of steroid or bronchodilators

ineffective for an acute attack

becomes effective over time (e.g. 2-3 weeks)

allergic rhinitis

atopic diseases of the eye

giant papillary conjunctivitis

Histamine Release Inhibitors

Dosage form

aerosol powder (Intal) and solution - asthma
nasal spray (Nasalcrom) - allergic rhinitis
optic solution 4% - (Opticrom) - allergic conjunctivitis

Toxicity

well tolerated, few adverse reactions
irritation due to powder inhalation
Stinging, Burning, Bad Taste
Coughing, sneezing, allergic reactions

Learning Objectives

- I Histamine
 - Pharmacological effects
 - Sites of action
 - Conditions which cause release
 - Diagnostic uses
- II Antihistamines acting at the H₁ and H₂ receptor
 - Pharmacological effects
 - Mechanisms of action
 - Therapeutic uses
 - Side effects and drug interactions
 - Be familiar with the existence of the H₃ receptor
- III Be able to describe the main mechanism of action of cromolyn sodium and its clinical uses

Practice Questions

- 1) Which of the following antihistamines is most likely to potentiate the CNS depressant effects of alcohol?
 - A. Promethazine (Phenergan)
 - B. Loratadine (Claritin)
 - C. Rantidine (Zantac)
 - D. Chlorpheniramine (Chlor-Trimeton)
 - E. none of the above
- 2) Rantidine (Zantac), an H₂ receptor antagonist, is **most** likely to produce which of the following effects?
 - A. inhibition of the "triple effect" of histamine
 - B. inhibition of gastric secretions
 - C. inhibition of nausea and vomiting
 - D. sedation
 - E. inhibition of salivary and bronchial secretions

Practice Questions

- 3) Which of the following statements about antihistamines are correct?
 - A. antihistamines prevent histamine release
 - B. antihistamines produce their effects through competition at the receptor
 - C. antihistamines promote histamine degradation
 - D. antihistamines prevent histamine synthesis
 - E. all of the above statements are correct
- 4) Which of the following effects is **NOT** associated with histamine?
 - A. triple effect
 - B. progressive fall in blood pressure
 - C. headache
 - D. secretion of catecholamines from chromaffin cells in adrenal medulla
 - E. sedation

Practice Questions

- 5) Which of the following drugs would be the best treatment for allergic rhinitis if you operated heavy machinery?
 - A. diphenhydramine (Benadryl)
 - B. nizatidine (Axid)
 - C. promethazine (Phenergan)
 - D. fexofenadine (Allegra)
 - E. rantidine (Zantac)
- 6) Nizatidine (Axid) an H₂ antagonist, can be effectively used for the control of _____.
 - A. itching associated with insect bites
 - B. asthma
 - C. indigestion
 - D. the triple effect
 - E. insomnia

Practice Questions

- 7) Antihistamines acting at the _____ receptor are most likely to _____.
 - A. H₁ receptor; inhibit the "triple effect" of histamine
 - B. H₂ receptor; inhibit the "triple effect" of histamine
 - C. H₁ receptor; reverse anaphylaxis
 - D. H₂ receptor; reverse anaphylaxis
 - E. H₁ receptor; block gastric secretions
- 8) Which of the following effects is **most commonly** associated with histamine?
 - A. progressive increase in blood pressure
 - B. progressive decrease in blood pressure
 - C. decrease in gastric secretions
 - D. triple effect
 - E. sedation