Antihistamines
Allergies

Characterized by a “local or systemic inflammatory response to allergens”

- Type I hypersensitivity
- Prevalence:
  - 1 in 4 people
  - 50 million Americans
  - Sixth leading cause of chronic disease
  - Healthcare system spends $18 billion a year
  - Higher in urban areas
The History of Allergies

- 1906 - von Pirquet discovered tissue reactivity to external stimulants, called it “allergies”
- 1921 - C. Prausnitz and H. Küstner found a connection between a serum factor, termed “reagine”, and allergies
- 1923 - A.F. Coca and R. Cooke introduced the term "atopy" to define a “constitutional status of predisposition to develop allergic diseases as pollinosis and bronchial asthma with a "reaginic" pathogenesis.”
- 1945 - Benadryl, first antihistamine introduced
- 1967 - two American researchers discovered a “reaginic” factor with high reactivity that they named Immunoglobulin E
- 1981 - Benadryl sold over the counter
- 1985 - first non-sedating antihistamine introduced
- 1993 - Claritin introduced
- 1996 - Allegra and Zyrtec introduced
Common Allergens

- Tree Pollen and Grass
- Pet Danders
- Mold
- Dust Mites
- Foods
Symptoms

- Allergic Rhinitis
- Conjunctivitis
- Bronchoconstriction
- Urticaria (gejala, biduran)
- Atopic Dermatitis (kelainan kulit kronis (menahun) yang meliputi ruam yang bersisik dan gatal)
- Anaphylaxis (reaksi alergi berat)

http://allergy.healthcentersonline.com/nasalsinus/allergicrhinitis.cfm
Histamine

- Signal involved in local immune response, also a neurotransmitter
- Synthesized by the decarboxylation of histidine
- Either stored or quickly inactivated by histamine-N-methyltransferase and diamine oxidase
- Release of histamine from mast cells is stimulated by IgE antibodies which respond to foreign antigens in the body
Histamine Receptors

- **H1 histamine receptor**
  - Found on smooth muscle, endothelium, and central nervous system tissue
  - Activation results in vasodilatation, bronchoconstriction, smooth muscle activation, and separation of endothelial cells.

- **H2 histamine receptor**
  - Found on parietal cells
  - Regulates gastric acid secretion

- **H3 histamine receptor**
  - Found in the central nervous system
  - Regulates the release of other neurotransmitters

- **H4 histamine receptor**
  - Recently discovered in different parts of the body including organs of the digestive tract, basophils, and bone marrow cells
An Allergic Reaction

- Early phase reaction: occurs within minutes of exposure to an allergen and lasts for 30-90 minutes
- Late phase reaction: begins 4-8 hours later and can last for several days, often leading to chronic inflammatory disease
An Overview of Antihistamines

• Reversible H1 receptor antagonists
• Also considered “Inverse Agonists”
• Block the binding of Histamine to its receptors
• Three generations of Antihistamines
  • Each generation improved on the previous one
  • Share general characteristics and properties
First Generation Antihistamines

- Small, lipophilic molecules that could cross the BBB
- Not specific to the H1 receptor
- Groups:
  - Ethylenediamines
  - Ethanolamines
  - Alkylamines
  - Piperazines
  - Tricyclics
- Common structural features of classical antihistamine
  - 2 Aromatic rings
  - Connected to a central Carbon, Nitrogen or CO
  - Spacer between the central X and the amine
  - Usually 2-3 carbons in length
  - Linear, ring, branched, saturated or unsaturated
  - Amine is substituted with small alkyl groups eg CH3
Second Generation Antihistamines

• Modifications of the First Generation Antihistamines to eliminate side effects resulted in the Second Generation Antihistamines
• More selective for peripheral H1 receptors
• Examples:
  • terfenadine
  • loratadine
  • cetirizine
  • mizolastine
  • astemizole
“Next” Generation Antihistamines

• Metabolite derivatives or active enantiomers of existing drugs
• Safer, faster acting or more potent than Second Generation drugs
• Examples:
  • Fexofenadine
  • Desloratadine
  • Levocetirizine
<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Target Symptoms</th>
<th>Adult Dose</th>
<th>Adverse Drug Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-generation antihistamine</td>
<td>Chlorpheniramine</td>
<td>Chlor-Trimeton</td>
<td>Sneezing</td>
<td>2-12 mg bid</td>
<td>Least sedating</td>
<td>Blurred vision, dry mouth, drowsiness, GI upset, urinary retention, nausea; avoid in patients with CVD, pregnancy, BPH, asthma, EtOH, sedatives, and anticholinergics</td>
</tr>
<tr>
<td></td>
<td>Clemastine</td>
<td>Tavist-1</td>
<td>Rhinorrhea Palatal itching</td>
<td>1.34 mg bid</td>
<td>Most sedating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>Benadryl</td>
<td>Ocular itching Nasal itching</td>
<td>25-50 mg q 6-8 h</td>
<td>Least sedating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brompheniramine</td>
<td>Various</td>
<td></td>
<td>4-8 mg tid-qid</td>
<td>Most GI upset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tripelennamine</td>
<td>PBZ</td>
<td></td>
<td>Up to 600 mg qd</td>
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<td></td>
</tr>
<tr>
<td>Second-generation antihistamine</td>
<td>Loratadine</td>
<td>Claritin</td>
<td>Sneezing Rhinorrhea Palatal itching</td>
<td>10 mg qd</td>
<td>Not as effective as first-generation drugs, but less sedating; no efficacy difference between any of the second-generation drugs (Rx vs OTC)</td>
<td></td>
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<tr>
<td>Systemic decongestant</td>
<td>Pseudoephedrine</td>
<td>Sudafed</td>
<td>Nasal congestion</td>
<td>30-60 mg q 4-6 h</td>
<td>Tachycardia, insomnia, palpitations, drowsiness, nervousness, HA, dizziness, weakness</td>
<td>Avoid in patients with HTN, DM, arrhythmias, glaucoma, BPH, hyperthyroidism, pregnancy/breastfeeding, MAOIs</td>
</tr>
<tr>
<td>Nasal decongestant</td>
<td>Xylometazoline</td>
<td>Otrivin</td>
<td>Nasal congestion</td>
<td>1-3 sprays bid</td>
<td>Burning, swelling, sneezing, stinging, increased discharge</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymetazoline</td>
<td>Afrin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular decongestant</td>
<td>Nephrizin</td>
<td>Clear Eyes</td>
<td>Removes redness from eye</td>
<td>1-2 drops up to 4x/d</td>
<td>Burning, stinging, transient pain, conjunctivitis, eyelid eczema/dermatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxymetazoline</td>
<td>Visine LR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Tetrahydrozoline</td>
<td>Visine</td>
<td></td>
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<tr>
<td>Nasal cromones</td>
<td>Cromolyn</td>
<td>NasalCrom</td>
<td>Sneezing Rhinorrhea Nasal congestion</td>
<td>1 spray tid-qid</td>
<td>Transient burning/stinging</td>
<td>1-2 wk of scheduled use to see benefit; warm in hand before use; must be discarded in 2-3 mo regardless of expiration date</td>
</tr>
</tbody>
</table>
Pharmacokinetics

• Second generation antihistamines:
  • Relatively rapid onset
  • Elimination Half-Lives:
    • Loratadine-up to 28 hours
    • Fexofenadine-14 hours
    • Cetirizine-8 hours
  • Children metabolize Cetirizine faster, but rates are similar for the others
Adverse Reactions and Side Effects

- **First Generation Drugs:**
  - Anticholinergic CNS interactions
  - Gastrointestinal reactions
  - Common side effects: sedation, dizziness, tinnitus, blurred vision, euphoria, lack of coordination, anxiety, insomnia, tremor, nausea and vomiting, constipation, diarrhea, dry mouth, and dry cough

- **Second Generation Drugs:**
  - Common side effects: drowsiness (ngantuk), fatigue, headache, nausea and dry mouth

- Side effects are far less common in Second Generation drugs
Prevalence that is steadily increasing worldwide

Partially attributed to increased awareness and diagnosis

Two Theories:
- “Hygiene” Theory
- Increasing Use of Chemicals
References:

http://en.wikipedia.org/wiki/Allergy


http://www.niaid.nih.gov/factsheets/allergystat.htm

http://erj.ersjournals.com/cgi/content/full/17/4/773

http://en.wikipedia.org/wiki/Histamine

“Safety and Efficacy of Desloratadine”


“Antihistamines as Important Tools for Regulating Inflammation”

http://www.jaoa.org/cgi/reprint/102/6_suppl/7S.pdf

http://en.wikipedia.org/wiki/Antihistamine