Pharmacology 659

Pulmonary Pharmacology

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Asthma

Symptoms:

• Recurrent shortness of breath, chest tightness, and wheezing, often with coughing.

Pathophysiology:

• Widespread, reversible narrowing of the bronchial airways
• Increased bronchial responsiveness to inhaled stimuli
• Lymphocytic, eosinophilic inflammation of the bronchial mucosa
• “Remodeling” of the bronchial mucosa with thickening of the lamina reticularis below the epithelium and hyperplasia of cells of all structural elements of the airway wall vessels, smooth muscle, and secretory glands and goblet cells.

Current Prevalence in Millions

<table>
<thead>
<tr>
<th>Age</th>
<th>Under 18</th>
<th>Over 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4.1</td>
<td>5.9</td>
</tr>
<tr>
<td>Female</td>
<td>2.7</td>
<td>10.2</td>
</tr>
</tbody>
</table>

| Current Prevalence in Millions |

Asthma prevalence by age and sex.
Hospitalization for types of respiratory diseases: Children under age 15, 2005

- All other diagnoses: 74%
- Respiratory Diseases: 26%
  - Pneumonia: 31%
  - Asthma: 25%
  - Acute bronchitis and bronchiolitis: 25%
  - All other Respiratory Diseases: 19%

Current Prevalence in Millions

Male
- 2001: 8.6
- 2002: 8.5
- 2003: 8.2
- 2004: 8.9
- 2005: 9.1
- 2006: 10.0

Female
- 2001: 11.7
- 2002: 11.6
- 2003: 11.6
- 2004: 11.6
- 2005: 13.1
- 2006: 12.8

Graph shows the trend in asthma prevalence by gender from 2001 to 2006.
Causes of Airway Narrowing

• Contraction of bronchial smooth muscle
• Inspissation of viscid mucus plugs
• Thickening of bronchial mucosa from edema, cellular infiltration, and hyperplasia of secretory, vascular, and smooth muscle cells.
Triggering Agents

• Respiratory infections and colds
• Cigarette smoke
• Allergens such as pollen, mold, animal dander, feathers, dust, food and cockroaches
• Exercise
• Exposure to cold air or sudden temperature change
• Odors and fumes
• Excitement or stress
Immunopathogenesis of asthma

- Smooth muscle
- Blood vessel
- Cell infiltration

**Early reaction**

- Airway wall
- Mast cell
- Tryptase
- PGD₂
- LTC₄
- PAF
- IL-4
- IL-5
- GM-CSF
- TNF
- TGF

**Late reaction**

- Mast cell
- T lymphocyte
- Eosinophil
- Neutrophil
- ECP
- MBP
- Proteases
- PAF
Inhaled irritant
Sensory receptors
Vagal efferent
Vagal afferent
Airway
CNS
Postganglionic neuron
Transmitter (ACh)
Lumen
Mediators from response cell
Tissue response cells (mast cell or eosinophil)
Smooth muscle cells
Inhaled irritant
Mucosa
Lumen
Sensory receptors
Short-term Relief

• β-Adrenergic Agonists
• Theophylline, a methylxanthine drug
• Antimuscarinic agents
Long-term Control

• Inhaled corticosteroid
• Leukotriene antagonist
• Inhibitor of mast cell degranulation
• Humanized, monoclonal antibody, omalizumab
Bronchial tone

Bronchodilation

Bronchoconstriction

Muscarinic Antagonists

Acetylcholine

Theophylline

Adenosine

Beta agonists

Theophylline

ATP

cAMP

AMP

AC

PDE

+ 

- 

+ 

- 

+ 

- 

+ 

- 

- 

+ 

- 

+ 

- 

Theophylline

Promoted bronchodilation
β-Adrenergic Agonists

• Relax bronchial smooth muscle
• Inhibit mast cell release of histamine, etc.
• Inhibit microvascular leakage
• Increase mucociliary transport
• Increase intracellular cAMP
β-Adrenergic Agonists

- Albuterol
- Terbutaline
- Metaproterenol
- Salmeterol
- Isoproterenol
- Epinephrine
- Ephedrine
β-Adrenergic Agonist Cautions

• Cardiac arrhythmias
• Hypoxemia
• Tachyphylaxis
• Genetic variation
Methylxanthines

• Inexpensive
• Phosphodiesterase inhibitors
• Adenosine receptor blockers
• Enhancement of histone deacetylation
Methylxanthines

• CNS stimulants
• Positive chronotropic and inotropic effects on heart
• Stimulate gastric secretion of acid and digestive enzymes
• Weak diuretics
• Bronchodilation
• Enhance skeletal muscle contraction
Methylxanthines

• Improves long-term treatment of asthma when taken as the sole maintenance treatment
• Inexpensive
• Orally administered
• Plasma levels must be monitored
Muscarinic Blocking Drugs

• Ipratropium bromide, tiotropium
• Poor absorption
• Can be administered by inhalation
• Especially good in patients with COPD
Corticosteroids

- Antiinflammatory
- Administration by inhalation reduces toxicity
- Are not curative
Corticosteroids

• Beclomethasone
• Budesonide
• Ciclesonide
• Flunisolide
• Fluticasone
• Mometasone
• Triamcinolone
Mast Cell “Stabilizers” – Cromolyn & Nedocromil

• Inhibit antigen and exercise-induced asthma
• Have no effect on bronchial smooth muscle tone
• Will not reverse bronchospasm
• Only useful for prophylaxis
Leukotrienes

• Are arachidonic acid derivatives
• Synthesized by eosinophils, mast cells, macrophages, and basophils
• Cause bronchoconstriction
• Increase bronchial reactivity to histamine
Leukotriene Blockers

• Zileuton, 5-lipoxygenase inhibitor
• Zafirlukast, LTD₄-receptor antagonist
• Montelukast, LTD₄-receptor antagonist
Anti-IgE Monoclonal Antibodies -
Omalizumab

• Inhibits IgE binding to mast cells
• Used in patients with severe asthma
• Extremely expensive
Chronic Obstructive Pulmonary Disease

- Airflow limitation not fully reversible with bronchodilator treatment
- Occurs in older patients
- Neutrophil rather than eosinophil inflammation
- Poorly responsive to corticosteroids
- Progressive loss of pulmonary function over time
- Associate with cigarette smoking.
Chronic Obstructive Pulmonary Disease

• Routine treatment is with antibiotics!