Objectives

- Discuss purpose of respiratory pharmacology
- Review terminology related to pharmacology
- Describe the central and peripheral nervous system
- Classify and describe the most commonly used drugs in respiratory care
- Identify the classes of drugs in the each step of asthma management

Purpose

- Relieve the “pathologic triad”:
  - bronchospasm
  - retained secretions
  - mucosal edema
- Agents used to treat the symptoms are called the “treatment triad”:
  - bronchodilators
  - mucokinetic agents
  - anti-inflammatory agents

Terminology

- Receptor- a location on a cell where reversible bonds are formed with a specific drug (lock and key).
- Affinity- the tendency a drug has to combine with a receptor site
- Agonist- A drug that has affinity and produces an effect
- Partial agonist- A drug that has affinity but cannot produce a full effect
- Antagonist- A drug that has affinity but produces no effect
- Efficacy- The ability of a drug to produce an effect
- Potency- The quantity of drug required to produce an effect determines potency

The Nervous System

- Central Nervous System (CNS) - The brain and spinal cord
- Peripheral Nervous System- Nerve pathways outside the CNS, divided into two parts
Peripheral Nervous System

- Afferent Pathways - Conduct information to the CNS
- Efferent Pathways - Conduct information away from the CNS, divided into two parts
  - Somatic - under conscious control
  - Autonomic - controls involuntary bodily functions, divided into two parts

Peripheral Nervous System

- Autonomic nervous system
  - Sympathetic - designed to protect the integrity of the organism and produces the "fight or flight" response
  - Parasympathetic - concerned with conservation of energy and restoration of function. Slows down and minimizes organ function
  - "Tone" is possible by exertion of opposite forces

Sympathetic Receptors

- Alpha - stimulation results in vasoconstriction, slight bronchoconstriction, reflexive decrease in heart rate (alpha agonist)
- Beta 1 - stimulation results in increased heart rate (beta 1 agonist)
- Beta 2 - stimulation results in bronchodilation (beta 2 agonist)

Respiratory Pharmacology

- Beta 2 Adrenergic
- Alpha Adrenergic
- Cholinergic Drugs

Drugs that stimulate sympathetic receptor sites (alpha, beta 1, beta 2) are also known as:

- Sympathomimetics
- Adrenergics
- Catecholamines

Also Known As:

- Sympathomimetics
- Adrenergics
- Catecholamines

Bronchodilators: Inhaled Beta₂-agonists

- Rapid onset of action, 10-15 minutes
- Maximum duration 4-6 hours
- Smooth muscle relaxation
- Most effective on an "as needed" basis
- Can both prevent and reverse exercise-induced bronchospasm
- Treatment of choice for mild asthma and acute exacerbations
Potential Problems with Inhaled Beta₂-agonists

- Regular use (more than one cannister/month) is associated with diminished control of asthma
- Relieves symptoms but does not control underlying inflammation

Adrenergic Bronchodilators

- Have become increasingly beta 2 selective to decrease cardiac side effects
  - Ventolin, Proventil
  - Alupent
  - Brethine
  - Bronkosol
  - Maxair
  - Bitolterol
  - Xopenex
  - Serevent
  - Foradil
  - Albuterol Sulfate
  - Metaproterenol Sulfate
  - Terbutaline Sulfate
  - Isethanrine
  - Pirbuterol
  - Tornalate
  - Levalbuterol (Albuterol)
  - Salmeterol (Serevent)
  - Formoterol (Long Acting)

Xopenex (Levalbuterol)

Manufacturer:
- Abbott Laboratories, Sepracor Inc

Levalbuterol or Xopenex is the R isomer of salbutamol (racemic albuterol)

The word racemic means that the drug has two sides or two drugs in equal amounts which are labeled R and S

Xopenex (Levalbuterol)

Salbutamol (albuterol) is a mixture of two isomers - R and S

- It is thought that the R isomer is the more active compound and that the S isomer contributes to some of salbutamol's side effects
- The S-albuterol should be viewed as a contaminate and has been shown to deteriorate lung function as early as 4 weeks.

Xopenex (Levalbuterol)

**Dosage:**
- Each 3 mL unit-dose vial contains either 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl).

**Frequency:**
- TID (every 6 to 8 hours) by nebulization

Racemic formoterol (RR,SS-formoterol)

- Similar to Xopenex
- Available outside the US, but currently under FDA investigation
Long-Acting Inhaled B2-agonist

- Formoterol is a full B2 agonist
  - Has more rapid onset than salmeterol
- Salmeterol is a partial B2 agonist
  - Clinical significance is unclear
- Should **always** be combined with inhaled steroids
  - Available in combination therapy inhalers
- Better as add-on therapy vs increasing inhaled steroid dose 2-fold or more

Parasympathetic stimulation

- Parasympathomimetics or cholinergics stimulate parasympathetic sites
- Parasympatholytics and anticholinergics block stimulation of parasympathetic receptor sites

Respiratory Pharmacology

- Block parasympathetic receptors, thus increase sympathetic tone:
  - Atrovent
  - Atropine
  - Robinul
  - Spiriva (24 hour)

Anticholinergic Bronchodilators

- Asthma management-exacerbations only
- Ipratropium Bromide
- Atropine Sulfate
- Glycopyrolate
- Tiotropium

Xanthine Bronchodilators

- Maintain cAMP levels by inhibiting phosphodiesterase:
  - Caffeine
  - Theophylline
  - Theobromide
  - Aminophylline contains theophylline and may improve diaphragmatic function

Respiratory Pharmacology
Methylxanthines
- Phosphodiesterase inhibitors at high concentrations (> 10 mg/l)
- Anti-inflammatory effect at lower concentrations (5-10 mg/l)
- Less effective as add-on therapy than long-acting inhaled B2-agonist
- Inexpensive
- Serum levels: 5-15 ug per ml
- Pregnancy, febrile illness, liver disease, CHF, and drugs cimetidine, quinolones, macrolides, cause reduced clearance mechanism

Asthma Inflammatory Response
- Allergen
- TH2 Lymphocyte
- Mast Cell
- Plasma Cell
- Eosinophil

Histamine
- Leukotrienes
- Thromboxane
- Cytokines
- Bronchospasm
- Cell migration
- Amplification
- Secretion

Anti-inflammatory Agents
- Glucocorticoids-
  - Cause a reduction in the markers of airway inflammation in airway tissue / airway secretions
  - Decrease the intensity of airway hyperresponsiveness.
  - Decrease vascular congestion and cellular infiltration
  - May be given topically by inhaler or systemically
  - Systemic steroids have more adverse effects such as:
    - Increased blood sugar
    - Depletion of bone calcium
    - Increase in fat production
    - Immunologic impairment
    - Hypertension

Inhaled Corticosteroids
- Potent local anti-inflammatory with minimal systemic toxicity
- Chronic use decreases airway hyperresponsiveness
- Block late reaction to allergen and reduce airway hyperresponsiveness
- Inhibit cytokine production, adhesion protein activation, inflammatory cell migration, and activation
Local Side Effects
- Oral thrush - prevalence increased when inhaled and oral combined
- Cough - irritative
- Hoarseness
- Can be reduced by using spacer and rinsing mouth after each use
- Systemic Side Effects
- Infrequent at currently recommended doses
- Mild adrenal suppression possible with high doses

Systemic Corticosteroids (oral)
- Therapy of choice in uncontrolled moderate and severe disease
- Short course “bursts” (10-14 days) produce minimal side effects
- Dosage options:
  - Daily lowest possible dose
  - Every other day in the morning
  - Combined with inhaled
- Replaced by inhaled
- Medications to reduce corticosteroid dependency
  - Cromones (Cromolyn sodium, nedocromil)
  - Second generation antihistamines- loratidine
  - Methotrexate
**Non-steroidal Anti-inflammatory**

- Prevent the release / activity of chemical mediators
  - Intal: Cromolyn Sodium
  - Tilade: Nedocromil Sodium
  - Accolate: Zafirlukast
  - Singular: Montelukast
  - Zyflo: Zileuton

**Cromolyn Sodium - Intal**

- Non-steroidal
- Inhibits IgE mediated mediator release from mast cells (prevents degranulation)
- Effective prophylactically for both early and late phase reactions
- Patients response cannot be reliably predicted
- 4-6 week trial therapy may be required
- Minimal local side effects – cough
- Effective for cold air exercise induced bronchospasm

**Nedocromil Sodium - Tilade**

- Non-steroidal anti-inflammatory
- Inhibits early and late phase bronchoconstriction responses to allergens
- Daily maintenance therapy improves lung function, prevents or lessens symptoms, and reduces non-specific airway hyper-responsiveness
- Side effects are uncommon - include unpleasant taste, nausea, and vomiting
- Only available in metered-dose inhaler

**Leukotriene Pathway**

**Clinical Benefit**

- **Leukotriene modifiers**: Clinical benefits of monotherapy with leukotriene modifiers have been shown in children older than age 2. Leukotriene modifiers reduce viral induced asthma exacerbations in children ages 2-5 with a history of intermittent asthma. No safety concerns have been demonstrated from the use of leukotriene modifiers in children.
Leukotrienes

- Produced from arachidonic acid using lipoxygenase
  - Limited to cells of lung, blood vessels, epicardium
- Slow-reacting substance (SRS)
  - Noted for prolonged smooth muscle contraction
  - SRS-A found to be LTC4, LTD4, and LTE4
- Potent constrictors of bronchial smooth muscle
  - 1000-10,000x more potent than histamine or prostaglandin
  - Probable role in asthma

Cysteinyl Leukotrienes

- LTC4, LTD4, LTE4 (SRS-A)
- LTC4 & LTD4 (most potent)
  - Smooth muscle contraction, increase vascular permeability
- LTE4 (10% as potent as LTD4)
- All bind to receptor CysLT1

LTB4

- Chemotactic for neutrophils and eosinophils

Accolate (zafirlukast)

Dosing
- Adults and children 12 years of age and older—20 milligrams (mg) two times a day, on an empty stomach, at least 1 hour before or 2 hours after meals.
- Children between 7 and 11 years of age—10 milligrams two times a day, on an empty stomach, at least 1 hour before or 2 hours after meals.
- Children up to 7 years of age—Use and dose must be determined by your doctor.

Singulair (montelukast)

DOSAGE AND ADMINISTRATION

Adolescents and Adults 15 Years of Age and Older
- The dosage for adolescents and adults 15 years of age and older is one 10-mg tablet daily to be taken in the evening.

Pediatric Patients 6 to 14 Years of Age
- The dosage for pediatric patients 6 to 14 years of age is one 5-mg chewable tablet daily to be taken in the evening. No dosage adjustment within this age group is necessary.
Singulair

- **Pediatric Patients 2 to 5 Years of Age**
  - The dosage for pediatric patients 2 to 5 years of age is one 4-mg chewable tablet daily to be taken in the evening. Safety and effectiveness in pediatric patients younger than 2 years of age have not been established.

- The safety and efficacy of SINGULAIR was demonstrated in clinical trials where it was administered in the evening without regard to the time of food ingestion. There have been no clinical trials evaluating the relative efficacy of morning versus evening dosing.

Zyflo (zileuton)

- **5-Lipoxigenase Inhibitor**

  **Dosage**
  - Adults: 1 tab 4 times daily (600 mg each)
  - Children: Not recommended

  **Contraindications**: Active liver disease.
  Transaminase level ≥3xULN

  **Interactions**: Potentiates theophylline (reduce dose of theophylline by about one-half)

Mucolytics

- Either break down mucoproteins:
  - Mucomyst  Acetylcysteine

- *Or depolymerize long DNA chains into smaller ones:
  - Dornase Alpha  Pulmozyme

  *30-70% of the solid matter in purulent secretions is DNA

Comparison Of Anti-Leukotrienes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Dose</th>
<th>Drug Interactions</th>
<th>Adverse Effects</th>
<th>Other Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast (Singulair, Merck and Co., Inc.)</td>
<td>LTD4 receptor antagonist</td>
<td>³ 15 years: 10mg tablet once daily in the evening</td>
<td>None currently known</td>
<td>Possibility of Churg-Strauss syndrome in patients withdrawn from oral corticosteroids</td>
<td>None</td>
</tr>
<tr>
<td>Montelukast (Singulair, Merck and Co., Inc.)</td>
<td>LTD4 receptor antagonist</td>
<td>6 to 14 years: 5mg tablet once daily in the evening</td>
<td>None currently known</td>
<td>Possibility of Churg-Strauss syndrome in patients withdrawn from oral corticosteroids</td>
<td>None</td>
</tr>
<tr>
<td>Montelukast (Singulair, Merck and Co., Inc.)</td>
<td>LTD4 receptor antagonist</td>
<td>2 to 5 years: 4 mg tablet once daily in the evening</td>
<td>None currently known</td>
<td>Possibility of Churg-Strauss syndrome in patients withdrawn from oral corticosteroids</td>
<td>None</td>
</tr>
<tr>
<td>Zafirlukast (Accolate, Zeneca Pharmaceuticals)</td>
<td>LTD4 receptor antagonist</td>
<td>³ 12 years: 20mg tablet twice daily</td>
<td>Caution in patients receiving warfarin and possibly theophylline</td>
<td>Possibility of Churg-Strauss syndrome in patients withdrawn from oral corticosteroids</td>
<td>Doses must be administered one hour before or two hours after meals</td>
</tr>
<tr>
<td>Zileuton (Zyflo Filmtabs, Abbott Laboratories)</td>
<td>Lipoxygenase enzyme inhibitor</td>
<td>³ 12 years: 600mg four times daily</td>
<td>Caution in patients receiving warfarin, theophylline, and propranolol</td>
<td>Serum transaminase elevations</td>
<td>Liver function tests should be monitored before beginning treatment, every month for the first 3 months and every 3 months for the remainder of 1 year.</td>
</tr>
</tbody>
</table>

Anti-IgE Therapy

- **Xolair (Omalizumab)** is indicated for:
  - adults and adolescents (12 years of age and above) with moderate to severe persistent asthma **and**
  - who have a positive skin test or **in vitro** reactivity to a perennial aeroallergen **and**
  - whose symptoms are inadequately controlled with inhaled corticosteroids
Anti-IgE Therapy (Xolair, omalizumab)

- Anti-IgE binds IgE and removes it from circulation
- Xolair inhibits the binding of IgE to the high-affinity IgE receptor (Fc RI) on the surface of mast cells and basophils
- Limits the degree of release of mediators of the allergic response

Xolair (Omalizumab) 150 to 375 mg is administered SC every 2 or 4 weeks

- Because the solution is slightly viscous, the injection may take 5-10 seconds to administer
- Doses (mg) and dosing frequency are determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg).

Classification of Asthma Control

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controlled</th>
<th>Partially Controlled</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise tolerance</td>
<td>None</td>
<td>One to two times per week</td>
<td>More than three times per week</td>
</tr>
<tr>
<td>Limitations of activity</td>
<td>None</td>
<td>One to two times per week</td>
<td>More than three times per week</td>
</tr>
<tr>
<td>Need for inhaled or oral steroids</td>
<td>None</td>
<td>One to two times per week</td>
<td>More than three times per week</td>
</tr>
<tr>
<td>Long-term (IN and IN)</td>
<td>None</td>
<td>One to two times per week</td>
<td>More than three times per week</td>
</tr>
</tbody>
</table>

Fig. 4.3-1: Levels of Asthma Control

Part 4: Establish Medication Plans for Long-Term Asthma Management

- Intermittent Asthma
  - No daily medication recommended
  - PRN rapid acting Beta2 agonist
  - Patients with intermittent asthma who have severe exacerbations should be treated as moderate persistent asthmatics
Part 4: Establish Medication Plans for Long-Term Asthma Management

- **Mild Persistent Asthma**
  - Controller medication everyday
  - Inhaled steroid preferred
    - Sustained-release theophylline, cromones, or a leukotriene modifier are other options

- **Moderate Persistent Asthma**
  - Regular treatment with a combination of inhaled steroid and a long-acting inhaled beta2 agonist twice daily
  - Sustained-release theophylline or a leukotriene modifier may be used in lieu of the beta2 agonist
  - An alternative to combination therapy is a higher dose of inhaled steroid.

- **Severe Persistent**
  - Inhaled steroid at higher doses plus a long-acting beta2 agonist twice daily
  - Alternatives to the long-acting beta2 agonist for add-on treatment are an oral sustained-release theophylline, leukotriene modifier, or oral beta2 agonist
  - These alternatives may be added to the combination therapy
  - Gradual reductions may be attempted after 3 months of control is achieved