Asthma - Pharmacology

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
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Objectives

- Understand the epidemiology and pathophysiology of asthma
- Understand the MOA for medications used to treat asthma
- Understand the adverse effects associated with asthma medications and be able to differentiate between local and systemic adverse effects
- Know the difference between the drugs to treat asthma exacerbation vs the drugs to prevent asthma exacerbation
Asthma

Chronic inflammatory disorder of the airways in which many cells and cellular elements play a role: in particular, mast cells, eosinophils, neutrophils (especially in sudden onset, fatal exacerbations, occupational asthma, and patients who smoke), T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment.
Remember – What nerves are involved lung function?

<table>
<thead>
<tr>
<th>Muscarinic</th>
<th>Beta 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rest and digest</td>
<td>• Fight or flight</td>
</tr>
<tr>
<td>• Smooth muscle constriction</td>
<td>• Smooth muscle relaxation</td>
</tr>
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</table>
Asthma

- > 22 million Americans
- Common amongst children
  - Young children = boys > girls
- Ethnic differences
  - African Americans 39% higher prevalence over Caucasians
  - Hispanic less likely to be hospitalized
- Healthcare system burden
  - 2006, > 11 million ambulatory care visits
- Economic burden
  - > 19 billion in the US
Asthma – Children, adults, and smoking

- Pediatric asthma
  - Usually diagnosed by 5 years age
  - 30-70% will outgrow asthma by adulthood

- Predictors of adult asthma
  - Atopy
  - Onset during school age
  - Presence of BHR – (Bronchial Hyper-responsiveness)

- Morbidity and mortality
  - Acute exacerbations
  - Inadequate assessment
  - Deaths are 80-90% preventable
Causes of asthma - Etiology

- Genetics
  - 60-80% of the susceptibility
    - Air we breathe, GERD, Post nasal drip
- Innate immunity – The hygiene hypothesis
  - Exposure to infection early in life
  - Less frequent use of antibiotics
  - Most important for ages 0-2 yrs
- Environmental Risk factors
  - Socioeconomic status, family size, exposure to second hand smoke in infancy and in utero, allergen exposure, urbanization, respiratory syncytial virus infection, and decreased exposure to common childhood infectious agents
Pathophysiology

- Airflow limitation
  - Bronchoconstriction
  - Airway hyper-responsiveness
  - Airway edema
- Acute inflammation
- Chronic inflammation
Atopy

- Overly sensitive
  - Tendency to be hyper-allergic
- Atopy in asthma
  - Common
  - Systemic IgE
    - Immunoglobulin E – responsible for initiating an allergic reaction
      - Binds to allergens triggers mast cells to release substances that cause inflammation

Mast cells release HISTAMINE:
Dilates vessels making them more permeable than usual = swelling/inflammation
Histamine

- Inflammatory cytokine
  - Swelling
  - Redness
  - Heat

Increase of blood flow to the area of release - locally
TH$_1$ and TH$_2$ Cells

- TH$_1$ cells vs TH$_2$ cells
  - TH$_1$- Patients may need exposure to stimuli
  - TH$_2$- More during neonatal phase (amount of imbalance may determine allergenicity)
Leukotrienes

- Inflammatory cytokine

**CYTOKINES** (Histamine)

**POSPHOLIPASE A2**

**ARACADONIC ACID**

**LIPOXYGENASE**
- LTB4
  - Attracts Neutrophils
  - Bronchoconstriction
- Others
  - Arterial dilation/Increased venule permeability

**CYCLOOXYGENASE**
- Others
- PGE2
  - Fever & Pain
Early and Late Phase Allergic Reaction

- **Early phase reaction**
  - IgE
    - Macrophages, mast cells, & pro-inflammatory mediators
  - Contraction of airway smooth muscle
  - Mucus secretion
  - Vasodilation

- **Late phase reaction**
  - 6-9 hrs after provocation
  - Recruitment of more cells
  - Enhancement of nonspecific BHR
Chronic consequences

- Airway remodeling
- Increased fibrosis
- Increased inflammatory cells
- Increased muscle thickness
- Increased mucus
Drug Targets

• Inflammation
  • Mast cells
  • Leukotrienes
• SNS
• PNS
Medications

- Long-term preventative medication
  - Corticosteroids
  - Mast cell stabilizers
  - Leukotriene modifiers
  - Theophylline
  - LABAs (long-acting beta agonists)
  - Omalizumab

- Rescue medications
  - SABAs (short acting beta agonists)
  - Systemic corticosteroids
  - Anticholinergics
Long-term/preventative medications

- **Corticosteroids**
  - Anti-inflammatory actions (potent locally)
  - Inhaled
  - Preferred long-term control medication
  - **Dosing**
    - Daily, **BID**, TID, or QID
    - Improve 1-2 weeks
    - Max effects 4-8 weeks
    - Use bronchodilator first

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<th>Medium dose (mcg)</th>
<th>High dose (mcg)</th>
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Long-term/preventative medications

- Corticosteroids
  - Encourage use of spacers
    - Decrease oral bioavailability
  - Rinse and spit
    - Avoid thrush (candidiasis)
  - Adverse effects
    - Systemic & long-term
      - Growth suppression, osteoporosis, skin thinning, adrenal crisis
    - Adrenal suppression
  - Monitor – respiratory function & lung sounds, blood/urine glucose, & signs of adrenal suppression

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Long-term/preventative medications

- **Mast cell stabilizers** – Cromolyn
  - Prevents mast cells from releasing histamine, leukotrienes, and substances of anaphylaxis – inhibits bronchoconstriction
    - Oral and inhalation dosage forms
    - ADRs – Dizziness, headache, unpleasant taste, diarrhea, rash, fever
    - No oral bioavailability
    - Very nontoxic
    - Start with QID therapy that may be reduced to TID
    - Monitor – Pulmonary function tests (PFT), lung sounds and respiratory function
    - Not a rescue
Long-term/preventative medications

Leukotriene modifiers

- Reduce allergen, exercise, cold air, irritant, & ASA induced asthma
- Effective orally and may be administered once or twice a day
- ADRs – Headache, dizziness, diarrhea, arthralgia, fever, infection (geriatric)
- Not for rescue

- 5-lipoxygenase inhibitor
  - Zileuton
- Limited clinical use
  - Elevated liver enzymes
  - Inhibition of CYP3A4
- Dosed BID

- Leukotriene receptor angatonists
  - Montelukast and zafirlukast
- Dosed daily or BID
- Generally well tolerated
  - Rarely cause a syndrome similar to Churg-Strauss
  - Some reports of neuropsychiatric events
  - Zarfirlukast

- Hepatic failure
Long-term/preventative medications

- Methylxanthines
  - Moderately potent bronchodilator, antagonist against bronchospasm, mild anti-inflammatory properties
  - Oral
    - Theophylline sustained release
    - Injection: Aminophylline
  - Limited clinical use due to
    - Toxicities – competitive antagonist of adenosine (serum levels greater than 15 mcg/ml)
    - Drug interactions
  - Target serum concentrations
    - 5mcg/ml – most patients will experience bronchodilation
    - < 15 mcg/ml – most patients will NOT experience toxicity
    - > 15 mcg/ml – sharp and drastic rise in number of patients who experience toxicity
Long-term/preventative medications

• Methylxanthines
  • Types of toxic reactions
    • Nausea, vomiting, tachycardia, jitteriness, difficulty sleeping, to cardiac tachyarrythmias, and seizures
    • Has caused death at normal doses in children with viral illness
  • Routine blood concentrations essential
    • Eliminated by hepatic enzymes
      • CYP1A2, &CYP3A3
    • Clearance highly variable according to age
      • 1-9 year olds with the highest clearance
  • Less effective than ICS – no difference between sustained release beta 2 agonists, cromolyn, & LTRA
Long-term/preventative medications

- LABAs – Formoterol & salmeterol
  - Provide long acting bronchodilation by being more lipophilic than the SABAs and binding to the beta2 receptor for a longer duration
  - Inhaled or solution for nebulizer (formoterol)
  - Should NOT be used alone
    - No anti-inflammatory effects
    - Increased risk of asthma related death
  - Associated with tolerance
    - Diminished protective effect against methacholine, histamine, exercise challenge
    - Keeps bronchodilator response
  - ADRs – Nervousness, restlessness, chest pain, palpitations, arrhythmias, hyperglycemia, hypokalemia, tremor
  - Monitor – Cardiovascular effects
Long-term/preventative medications

- Omalizumab – Anti-IgE monoclonal antibody
  - Inhibits IgE from binding to mast cells and basophils and leads to a decrease in mediators in response to allergen exposure
  - Injection – sub Q
    - Slow absorption, peak effects in 3-14 days
  - Should be administered under medical supervision
  - Dose depends on baseline IgE
    - Usually range from 150-375 mg
    - Given Q 2-4 weeks
  - Approved to treat patients:
    - > 12 years of age
    - Have allergies
    - Severe persistent
    - Not adequately controlled with ICS/LABA combination
Quick relief/rescue medications

- **SABAs** – Albuterol, levalbuterol, pirbuterol
  - Works by binding to and activating beta 2 receptors in the lungs to relaxes airway smooth muscle thus opening up the airway
  - Inhaled (MDI or nebulizer solution), syrup, tablet, and extended release tablet
  - Treats acute symptoms (bronchospasm) of asthma including severe exacerbation and prevention of EIB
  - Bronchospasm
    - 2 puffs every 4-6 hours PRN
  - Acute exacerbation
    - 4-8 puffs every 20 minutes for up to 4 hours
  - Adverse drug effects – depends on age, dose, and ROA
    - Systemic: Hypokalemia, hyperglycemia, tachycardia, and cardiac dysrhythmias
  - Tolerance may occur but is easily overcome by initiating ICS therapy
Quick relief/rescue medications

- Systemic corticosteroids
  - Anti-inflammatory agents
  - Indicated in all patients with severe exacerbation not responding to SABA therapy
  - Parenteral forms are not more effective than oral forms
  - Should be continued until patient is at 70% of normal lung function
  - Tapering may not be required if patient is discharged on ICS
  - Prednisone 40-60 mg per day for 3-10 days
    - Outpatient courses of 3-5 days have been effective
  - Adverse effects
    - HPA axis suppression, HTN, headache, emotional instability, bruising, skin thinning, hyperglycemia
Quick relief/rescue medications

- **Anticholinergics**
  - Short acting
    - Ipratropium
  - Binds to muscarinic receptors in the lung to cause bronchodilation
  - When used with a SABA – will improve lung function another 10-15%
  - 2 puffs, QID also dosed PRN
  - ADRs
    - Dry mouth, Nausea, metallic taste
    - Poorly absorbed – minimal or no systemic effects
    - Inhaled MDI (nasal or oral) or nebulizer solution – combination products with albuterol
    - Take care to keep nebulizer solution out of the eyes
Questions