

Respiratory Pharmacology

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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

Terminology

- 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

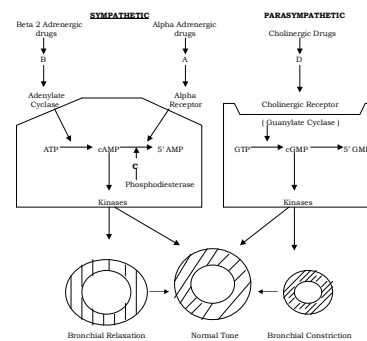
Peripheral Nervous System

- 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



Also Known As:

- Drugs that stimulate sympathetic receptor sites (alpha, beta 1, beta 2) are 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 Albuterol Sulfate
 - Alupent Metaproterenol Sulfate
 - Brethine Terbutaline Sulfate
 - Bronkosol Isoetharine
 - Maxair Pirbuterol
 - Bitolterol Tormalate
 - Xopenex Levalbuterol
 - Serevent Salmeterol
 - Foradil 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

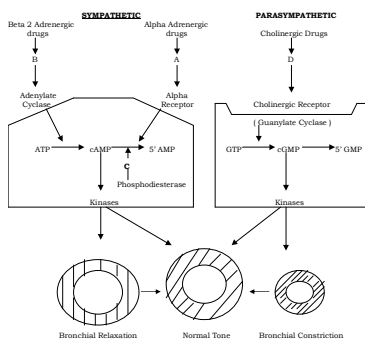
Long-Acting Inhaled B2-agonist

- 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



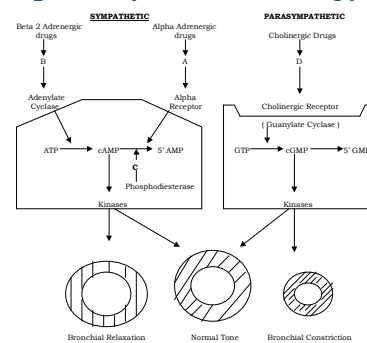
Anticholinergic Bronchodilators

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

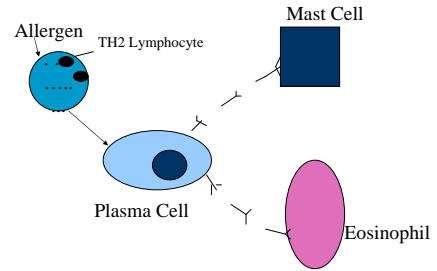
Respiratory Pharmacology



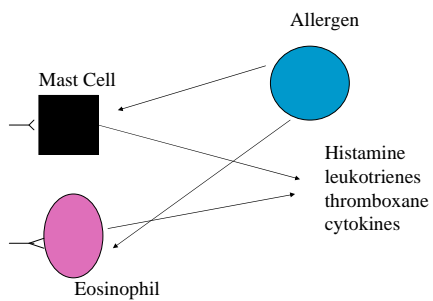
Methylxanthines

- 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



Asthma Inflammatory Response



Asthma Inflammatory Response

- | | | |
|----------------|---|------------------|
| ■ Histamine | → | ■ Bronchospasm |
| ■ leukotrienes | | ■ cell migration |
| ■ thromboxane | | ■ amplification |
| ■ cytokines | | ■ secretion |

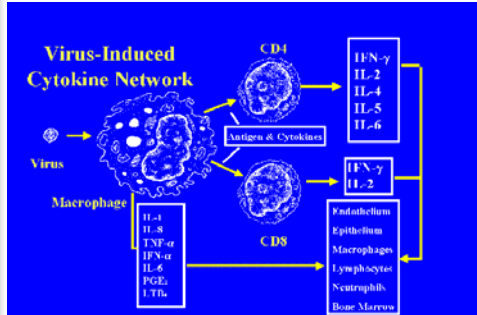
Anti-inflammatory Agents

- 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

Cytokine Network



Inhaled Corticosteroids(continued)

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

Steroids by MDI

- Azmacort, Kenalog
- Triamcinolone Acetonide
- Aerobid
- Flunisolide
- Beclovent, Vanceryl
- Beclomethasone
- Flovent
- Fluticasone
- Pulmicort
- Budesonide

Figure 3-1. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Adults[†]

Drug	Low Daily Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)‡
Beclomethasone dipropionate	200 - 500	>500 - 1000	>1000 - 2000
Budesonide*	200 - 400	>400 - 800	>800 - 1600
Ciclesonide*	80 - 160	>160 - 320	>320 - 1280
Flunisolide	500 - 1000	>1000 - 2000	>2000
Fluticasone	100 - 250	>250 - 500	>500 - 1000
Mometasone furoate*	200 - 400	>400 - 800	>800 - 1200
Triamcinolone acetonide	400 - 1000	>1000 - 2000	>2000

[†] Comparisons based upon efficacy data.

[‡] Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.

* Approved for once-daily dosing in mild patients.

Notes

• The most important determinant of appropriate dosing is the clinician's judgment of the patient's response to therapy. The clinician must monitor the patient's response in terms of clinical control and adjust the dose accordingly. Once control of asthma is achieved, the dose of medication should be carefully titrated to the minimum dose required to maintain control, thus reducing the potential for adverse effects.

• Designation of low, medium, and high doses is provided from manufacturers' recommendations where possible. Clear demonstration of dose-response relationships is seldom provided or available. The principle is therefore to establish the minimum effective controlling dose in each patient, as higher doses may not be more effective and are likely to be associated with greater potential for adverse effects.

• As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the equivalent correct dosage.

Figure 3-4. Estimated Equipotent Daily Doses of Inhaled Glucocorticosteroids for Children

Drug	Low Daily Dose (µg)	Medium Daily Dose (µg)	High Daily Dose (µg)†
Beclomethasone dipropionate	100 - 200	>200 - 400	>400
Budesonide*	100 - 200	>200 - 400	>400
Budesonide-Neb	250 - 500	>500 - 1000	>1000
Ciclesonide*	80 - 160	>160 - 320	>320
Flunisolide	500 - 750	>750 - 1250	>1250
Fluticasone	100 - 200	>200 - 500	>500
Mometasone furoate*	100 - 200	>200 - 400	>400
Triamcinolone acetonide	400 - 800	>800 - 1200	>1200

[†] Comparisons based upon efficacy data.

[‡] Patients considered for high daily doses except for short periods should be referred to a specialist for assessment to consider alternative combinations of controllers. Maximum recommended doses are arbitrary but with prolonged use are associated with increased risk of systemic side effects.

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• As CFC preparations are taken from the market, medication inserts for HFA preparations should be carefully reviewed by the clinician for the correct equivalent dosage.

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 } Cromones
 - Tilade Nedocromil Sodium
 - Accolate Zafirlukast } Leukotriene Modifiers
 - Singulair Montelukast
 - Zflo Zileuton

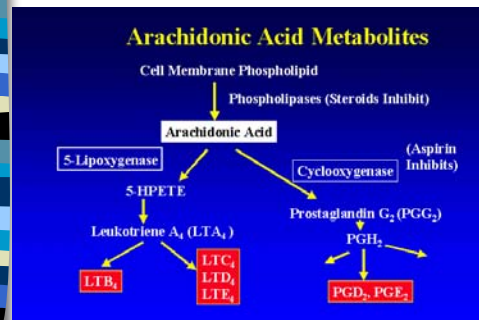
Cromolyn Sodium - Intal

- 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

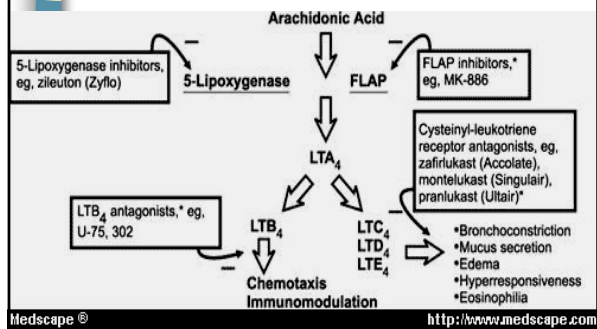
Nedocromil Sodium - Tilade

- 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



Anti-Leukotriene Drugs



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

Leukotrienes

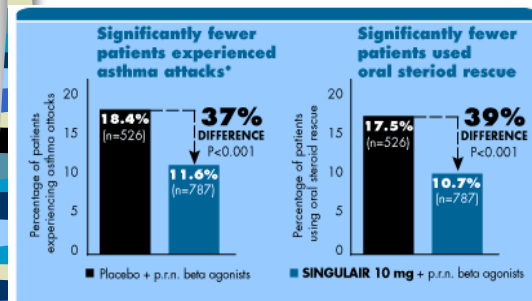
- Cysteinyl Leukotrienes
 - LTC₄, LTD₄, LTE₄ (SRS-A)
 - LTC₄ & LTD₄ (most potent)
 - Smooth muscle contraction, increase vascular permeability
 - LTE₄ (10% as potent as LTD₄)
 - All bind to receptor CysLT₁
- LTB₄
 - Chemotactic for neutrophils and eosinophils

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)



Singulair

- **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.

Singulair

- *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.

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

Anti-IgE Therapy

- 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).

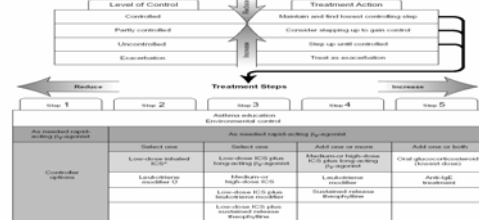
Classification of Asthma Control

Figure 4.3-1. Levels of Asthma Control

Characteristic	Controlled (All of the following)	Partly Controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/wakening	None	Any	
Need for reliever ¹ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV ₁) ²	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year ³	One in any week ⁴

¹ Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.
² By definition, an exacerbation in any week means that an uncontrolled asthma week.
³ Lung function is not a reliable test for children 5 years and younger.

Figure 4.3-2. Management Approach Based On Control For Children Older Than 5 Years, Adolescents and Adults



¹ ICS=inhaled glucocorticosteroids; LABA=long-acting beta₂-agonists; LTRA=leukotriene receptor antagonist or synthesis inhibitors.
² Add-on controller medications are either inhaled corticosteroids, short-acting beta₂-agonists, longer-acting beta₂-agonists, and short-acting muscarinic antagonists. Although an already well-controlled asthma may require no oral corticosteroids accompanied by regular use of an oral steroid, this is not recommended.

Figure 4.3-2: Management Approach Based on Control For Children 5 Years and Younger

The available literature on treatment of asthma in children 5 years and younger precludes detailed treatment recommendations. The best documented treatment to control asthma in these age groups is inhaled glucocorticosteroids and at Step 2, a low-dose inhaled glucocorticosteroid is recommended as the initial controller treatment. Equivalent doses of inhaled glucocorticosteroids, some of which may be given as a single daily dose, are provided in Chapter 3 (Figure 3-4).

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



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

■ 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.



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

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