RSPT 2317
Non-steroidal Anti-asthma Agents

Mechanisms of Inflammation in Asthma

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- Asthma is a chronic inflammatory disorder of the airways
- It is divided into extrinsic and intrinsic on the basis of triggers
  - extrinsic is dependent on allergy or atopy and is associated with younger subjects
  - intrinsic shows no evidence of sensitization to common, inhaled allergens and is associated with adults and later onset in which childhood asthma may not have been present
- Asthma has been described as an "evolving" disease in early childhood, when viruses are an important trigger, whereas in school and teen years, allergens stimulate an immune response

Mechanisms of Inflammation in Asthma

- As asthma progresses, and in adults, the disease becomes intrinsic and may be driven by T lymphocytes
- Asthma is chronic and persistent, with continual inflammation and episodes of acute obstruction. Three components of asthma are described as follows
  - the acute asthma attack, which resolves spontaneously or with treatment
  - a hyperresponsiveness of the airways to various stimuli
  - persistent inflammation

Mechanisms of Inflammation in Asthma

- In both forms, mediators and enzymes are released to act on target tissues
- Airway inflammation is manifested in the responses of bronchoconstriction, airway swelling, mucus secretion and obstruction

The Immunological (Allergic) Response

- The majority of asthma is primarily an allergic response that involves mast cells and immunoglobin E (IgE), essentially a mistaken immune response.
- The response is initiated by the interaction of T lymphocytes and an antigen
- Activation of these T lymphocytes results in the production of antigen-specific IgE, which binds to effector cells such as mast cells
- When activated by subsequent exposure to an antigen or allergen, mast cells release physiologically active mediators of inflammation, such as prostaglandins, leukotrienes, proteases, histamine, platelet-activating factor (PAF), and certain cytokines

The Immunological (Allergic) Response

- This cascade of mediators causes an inflammatory response manifested by vascular leakage, bronchoconstriction, mucus secretion and mucosal swelling
- T lymphocytes also release cytokines, causing accumulation and activation of eosinophils, which also release chemicals that damage the airway
- Once initiated by antigen exposure, the inflammatory process is amplified by chemoattraction of more lymphocytes, eosinophils, basophils and neutrophils and an increase in mast cells

The Immunological (Allergic) Response

- Antigen stimulation of lymphocytes and mast cells cause an increase in adhesion molecules, which in turn causes recruitment of more eosinophils, neutrophils and lymphocytes from the microvascular circulation into the airways. This further amplifies the inflammatory process. The increase and activation of eosinophils is associated with increased inflammation and severity in asthma
- Nonspecific stimuli such as fog, sulfur dioxide, dust and cold air can stimulate sensory receptors and cause reflexive bronchoconstriction. Asthmatic subjects are more sensitive to such stimuli due to either altered neural control or chronic inflammation sensitizing the airway, or both
- The release of neuropeptides and nitric oxide may also play a role in asthma

Mast Cell Stabilizing Agents

Cromolyn sodium

- Brand names
  - Intal (MDI; nebulizer solution), Nasalcrom (intranasal metered pump spray), Opticrom (eye drop solution), Gastrocrom (capsule with powder contents to be dissolved in hot water)
- Mode of action
  - inhibits the degranulation of mast cells by directly blocking the influx of calcium ions entering the mast cell, preventing the release of chemical mediators of inflammation
  - action is prophylactic and pretreatment is required
  - effective in blocking the late-phase reaction in asthma (more severe airway obstruction 6-8 hours after initial bronchoconstriction)

Cromolyn sodium

- Mode of action
  - does not have an antagonistic effect on any of the chemical mediators
  - does not operate through the cAMP system; does not affect α or β receptors
  - does not prevent antibody formation, IgE attachment to mast cells or the ag-ab union
- Indications
  - to decrease the frequency and intensity of asthma attacks in both allergic and nonallergic asthma
  - prevention of exercise induced asthma
  - treatment and prevention of allergic rhinitis and allergic conjunctivitis

Cromolyn sodium

- Contraindications
  - hypersensitivity to cromolyn, acute asthmatic attacks, status asthmaticus
- Precautions
  - not indicated in the treatment of acute asthmatic attacks or status asthmaticus; indicated only as a prophylactic agent
  - excreted in urine and bile (feces); therefore use with caution in pts. with impaired renal or hepatic function
  - safety and efficacy in children under age 5 and in pregnancy have not been established
  - if cough or bronchospasm occurs, pt. may not be able to continue tx; monitor pt. for symptoms and notify physician if coughing or wheezing occurs; prior use of a b2 adrenergic agonist should be used if a pt. develops bronchospasm and wheezing with the administration of cromolyn

Cromolyn sodium

- Adverse reactions
  - CNS: dizziness, headache
  - pulmonary: bronchospasm, wheezing, cough, laryngeal edema
  - miscellaneous: dermatitis, joint swelling, abdominal pain, sneezing, nasal congestion, epistaxis, urinary frequency, throat irritation or dryness
  - allergic: urticaria, rash, angioedema, anaphylaxis
- Clinical application
  - complete prophylactic activity may require 4-6 weeks

Cromolyn sodium

- Dosage forms
  - nebulizer solution: 20 mg/2 ml liquid ampule
  - MDI: 800 μg/actuation
  - nasal spray: 40 mg/ml
  - optical solution: 40 mg/ml
  - oral solution: 100 mg/capsule
- Dosage
  - nebulizer solution: adults and children ≥ 2 yrs.: 1 liquid ampule by SVN qid at regular intervals
  - MDI: adults and children ≥ 5 yrs.: 2 inhalations qid at regular intervals
  - nasal spray: adults and children ≥ 6 yrs.: 1 spray in each nostril q 4-6h
  - optical solution: as directed
  - oral solution: 200 mg qid (powder contents of capsule are dissolved in hot water)

Nedocromil sodium

- Brand name
  - Tilade
- Mode of action
  - inhibits mediator release from mast cells
  - inhibits eosinophil chemotaxis
  - does not have bronchodilator properties
  - optimum control of asthma symptoms depends on regular use, even if symptoms are not present
- Indications
  - to decrease the frequency and intensity of asthma attacks in both allergic and nonallergic asthma

Nedocromil sodium

- Contraindications
  - hypersensitivity to nedocromil, acute asthmatic attacks, status asthmaticus
- Adverse reactions
  - CNS: headache, dizziness
  - GI: unpleasant taste, nausea, vomiting
  - Cardiopulmonary: chest pain, cough, pharyngitis, rhinitis, bronchospasm, dyspnea, upper resp. tract infections
- Dosage form
  - MDI: 1.75 mg/actuation
- Dosage
- MDI: 2 inhalations qid

Leukotrienes and Inflammation

Leukotrienes and Inflammation

- Leukotrienes are members of a group of biologically active fatty acids known as *eicosanoids*
- These molecules are synthesized from arachidonic acid and are lipid mediators of inflammation that mediate directly or indirectly some of the inflammation seen in asthma
- Leukotrienes are potent bronchoconstrictors and stimulate other cells to cause airway edema, mucus secretion, ciliary beat inhibition and recruitment of other inflammatory cells into the airway

Leukotrienes and Inflammation

- Leukotrienes are not preformed; they are synthesized following a mechanical, chemical or physical stimulus, such as an antigen or allergen challenge
- Cells that have the necessary enzymes to synthesize leukotrienes include mast cells, eosinophils, basophils, neutrophils, monocytes, macrophages and B lymphocytes
- Leukotrienes bind to leukotrienes receptors to exert their inflammatory effects and several receptor types have been identified to date

Leukotrienes and Inflammation

- These receptors are involved in cellular recruitment (chemotaxis), probably of neutrophils, and may be involved in ARDS
- Stimulation of these receptors not only cause bronchoconstriction, but also an increase in bronchial hyperresponsiveness, increased mucus secretion and viscosity, increased vascular permeability causing airway edema and plasma exudation into the airway lumen

Clinical Use of Antileukotriene Agents

Clinical Use of Antileukotriene Agents

- Antileukotrienes are prophylactic controller drugs used in persistent asthma, including mild, moderate and severe states; they are not indicated for acute relief or rescue therapy
- Antileukotrienes are particularly useful in controlling asthma resulting from certain triggers, including exercise-induced asthma, aspirin-induced asthma, and to a lesser extent, allergen-induced asthma

Clinical Use of Antileukotriene Agents

- Antileukotrienes can be tried as an alternative to inhaled corticosteroids or cromolyn-like agents in mild persistent asthma requiring more than as-needed β_2 agonists
- Antileukotrienes may not be optimal as monotherapy in persistent asthma
- Antileukotrienes may allow reduction of high-dose inhaled corticosteroids or prevent an increase in the dose of inhaled corticosteroids and reduce or prevent the need for oral corticosteroids

Antileukotriene Agents

Zafirlukast

- Brand name
  - Accolate
- Mode of action
  - antagonizes leukotrienes receptors; blocks inflammatory effects of leukotrienes
  - action is prophylactic and regular use is required
- Contraindications
  - hypersensitivity to zafirlukast, or components of the formulation
- Administration
  - 1 hr. before or 2 hrs. after meal

Zafirlukast

- Drug interactions
  - theophylline, warfarin and aspirin
- Adverse reactions
  - headache, infection, nausea, possible liver enzyme changes
- Dosage forms
  - tablets: 20 mg
- Dosage
  - tablets: adults and children ≥ 12 yrs.: 1 tablet bid

Montelukast

- Brand name
  - Singulair
- Mode of action
  - inhibits the 5-LO enzyme, which is a catalyst for the formation of leukotrienes
  - action is prophylactic and regular use is required
- Contraindications
  - hypersensitivity to monteluskast, or components of the formulation, active liver disease or elevated liver enzymes
- Administration
  - can be taken with food

Montelukast

- Drug interactions
  - theophylline, warfarin and propranolol
- Adverse reactions
  - headache, dyspepsia, unspecified pain, liver enzyme elevations
- Dosage forms
  - tablets: 10 mg, 4 mg and 5 mg cherry-flavored chewable
- Dosage
  - tablets: adults and children ≥ 15 yrs.: one 10 mg tablet each evening
  - children 6-14 yrs.: one 5 mg chewable tablet each evening
  - children 2-5 yrs.: one 4mg chewable tablet each evening

Zileuton

- Brand name
  - Zyflo
- Mode of action
  - inhibits the 5-LO enzyme, which is a catalyst for the formation of leukotrienes
  - action is prophylactic and regular use is required
- Contraindications
  - hypersensitivity to zileuton, or components of the formulation, active liver disease or elevated liver enzymes
- Administration
  - can be taken with food

Zileuton

- Drug interactions
  - theophylline, warfarin and propranolol
- Adverse reactions
  - headache, dyspepsia, unspecified pain, liver enzyme elevations
- Dosage forms
  - tablets: 600 mg
- Dosage
  - tablets: adults and children ≥ 12 yrs.: 1 tablet qid