TREATMENT OF ASTHMA AND COPD

Jeopardy Game
- http://dev1.unmc.edu/JeopardyGame/gi.htm

ASTHMA

- Asthma is a disease associated with airway inflammation, airway hyperreactivity and acute bronchoconstriction.

- It is a complex disorder.
  - Both hereditary and environmental factors - allergies, viral infections, irritants - are involved in the onset of asthma and in the inflammatory episodes.

- A chronic inflammatory disease of the airways that is complicated by episodes of acute inflammation.
  - Inflammation is caused by allergens or other stimuli leading to bronchial hyperresponsiveness and obstruction of airflow.

- More than half of asthmatics have allergies; allergy to house dust mite feces is a major factor in the development of the disease and in the occurrence of exacerbations.
**ASTHMA**

- Attacks can be triggered by allergens, upper respiratory infection, increased rate of breathing, pollutants, NSAIDs and other factors.

- Nonallergic (intrinsic) asthma is more likely to occur when the disease first manifests during middle age (40 or older). It is generally severe.

**ASTHMA**

- Symptoms and pathology of asthma are due to release of mediators from inflammatory cells (mast cells, basophils, eosinophils and lymphocytes).

- The mediators produced by inflammatory cells infiltrating the asthmatic airway promote symptoms of airway narrowing thru smooth muscle contraction, airway edema, mucus secretion and bronchial hyperresponsiveness.

**MAJOR INFLAMMATORY MEDIATORS**

- Histamine - Rapidly released from activated mast cells; stimulates smooth muscle contraction and increased permeability, but other mediators have a greater impact.

- Leukotrienes - cause bronchoconstriction, stimulate mucus secretion etc.

- Prostaglandins - contraction of bronchial smooth muscle, increased vascular permeability and mucus secretion.

- Cytokines - recruitment and stimulation of additional inflammatory cells.
Triggers for mediator release

- Allergens
- Exercise
- Cold air
- Pollutants
- Drugs
- Viral respiratory infections
- Neuropeptides

ASTHMA

- Most asthmatics even those with mild disease show substantial airways inflammation.
- Inflammation, hypersecretion, airways hyperreactivity and bronchoconstriction are manifested by wheezing, coughing and breathing difficulty.

TWO PHASE RESPONSE

- Early phase (onset of 10 mins.)-rapid bronchoconstriction that persists 1-2 hrs.
- Due to release of preformed factors and lipid metabolites from bronchial mast cells; some of these directly stimulate smooth muscle contraction in the airways.

TWO PHASE RESPONSE

- Late phase (3-12 hrs)- more gradual and profound bronchoconstriction accompanied by edema, and mucus buildup; can persist for several hours.

TWO PHASE RESPONSE

- Due to release from mast cells during early response of various cytokines and lipid mediators that stimulate an influx of more inflammatory cells.
CONTROLLING ASTHMA

➢ Educating patients – regarding the factors causing asthma and the use of medications.
➢ Identifying and avoiding triggers that make asthma worse- known allergens (e.g. dust mites, cockroaches, fungi), environmental pollutants and aspirin and other cyclo-oxygenase inhibitors.

ASTHMA TREATMENT

➢ To prevent permanent destruction of lung tissue, treatment should begin early in the course of the disease.

ASTHMA TREATMENT

➢ Traditionally, asthma has been treated with bronchodilators, which help control the symptoms of asthma but do nothing for the inflammation.

CONTROLLING ASTHMA

➢ Treating asthma attacks (acute symptomatic relief).
➢ Managing asthma long term.

ASTHMA TREATMENT

➢ It is also important to treat associated disorders that exacerbate and are exacerbated by asthma such as allergic rhinitis, chronic sinusitis, nasal polyposis and anxiety.

ASTHMA TREATMENT

➢ Presently the focus is on treating the underlying inflammation as well as the bronchoconstriction.
AEROSOL DELIVERY OF DRUGS

- Metered Dose Inhalers
- Nebulizers
- Dry Powder Inhalers

ADRENERGIC RECEPTOR AGONISTS

- Include both the non-selective agonists like epinephrine and isoproterenol as well as the relatively selective $\beta_2$-agonists (e.g. albuterol and terbutaline).
**β- Adrenergic receptor agonists**

- Bind $\beta_2$ receptors on bronchial smooth muscle stimulating relaxation.

**EPINEPHRINE**

- Non-selective $\beta$-receptor agonist ($\beta_2$ action causes bronchodilation).
- Rapid but short-lived action in airways (30 min-1 hr).
- Used as an inhalant for relief of minor occasional symptoms.
- SC injection for severe asthmatic attacks.

**TOXICITY**

- Anxiety
- Tremors
- Tachycardia (effect on cardiac $\beta$-receptors).

**$\beta_2$-selective agonists**

- Classified as short or long-acting.
$\beta_2$ -selective agonists-short acting

- Albuterol (Proventil, Ventolin)
- Terbutaline (Brethaire)
- Levalbuterol (Xenopex)
- Pirbuterol (Maxair)
- Metaproterenol (Alupent)

PHARMACOKINETICS

- Usually delivered directly to the airways by inhalation.
- Rapid onset of action (1-5 mins).
- Duration is about 2-6 hrs.
- Oral preparations have a somewhat longer duration (6-8 hr).

THERAPEUTIC USES

- The most effective drugs available for treatment of acute bronchospasm and for prevention of exercise-induced asthma.

THERAPEUTIC USES

- Regular use of short acting agonists apparently offers no advantage over prn basis and may lead to tolerance.

ADVERSE EFFECTS

- Selective in their action so generally produce few side effects.

- Tachycardia, palpitations and tremor can occur at high doses.

ADVERSE EFFECTS

- CNS effects at higher doses.

- Overuse has been associated with an increase in mortality, but probably reflects worsening of the disease.
LONG ACTING β-ADRENERGIC RECEPTOR AGONISTS

- Salmeterol (SEREVENT)
- Formoterol (FORADIL AEROLIZER)

SALMETEROL

- Long duration of action (inhalation provides persistent bronchodilation lasting over 12 hrs.) with high β₂-receptor selectivity.

THERAPEUTIC USES

- Twice daily inhalation of salmeterol, has been effective for maintenance treatment and may be especially useful in patients with nocturnal symptoms.

THERAPEUTIC USES

- Sometimes added to steroid use (may be more favorable than doubling steroid dose).
- Slow onset and a prolonged effect so it is not recommended for treatment of acute bronchospasm.

THERAPEUTIC USES

- Patients taking it regularly should use a short-acting beta agonist as needed to control acute symptoms.
- Long term daily use may lead to receptor desensitization and a decreased effect.

ADVERSE EFFECTS

- Like other β₂ agonists it can cause tachycardia, palpitations, tremor and headache.
- No adverse interactions result from using it with inhaled corticosteroids.
FORMOTEROL
- Long acting beta_2_ agonist now approved for maintenance treatment of asthma and prevention of exercise-induced bronchospasm.
- Inhalation powder.
- Rapid onset of action.
- Like salmeterol taken twice daily.

ORAL \( \beta \)-AGONIST THERAPY
- Less effective, produce more adverse effects and have a slower onset of action.
- Oral syrup formulations may be useful for some young children with mild symptoms who can't use an inhaler and spacer.
- In some patients with severe asthma any aerosol can worsen cough and bronchospasm.

ORAL \( \beta \)-AGONIST THERAPY
- Greater risk of systemic side effects especially tremulousness, muscle cramps, cardiac arrhythmias and metabolic disturbances.

CORTICOSTEROIDS
- Antagonists of transcription factors that regulate increased transcription of genes involved in inflammation (e.g. inflammatory cytokines and enzymes in asthma).

CORTICOSTEROIDS - MECHANISM OF ACTION
- Do not relax airway smooth muscle and thus have little effect on acute bronchoconstriction.
- Bind to glucocorticoid receptors.
- Inflammatory processes inhibited at multiple levels.

Inhaled corticosteroids
\[ \text{Airway epithelial cells} \]
\[ \downarrow \text{NF-κB, AP-1} \]
\[ \downarrow \text{COX-2, PLA}_2 \]
\[ \downarrow \text{ICAM-1, RANTES} \]
\[ \downarrow \text{GM-CSF, Eotaxin, IL-1β} \]
\[ \downarrow \text{NO, PGs} \]
\[ \downarrow \text{INFLAMMATION} \]
INHALED STEROIDS

- All have similar mechanisms.
- All are equally effective with the appropriate dose.
- Fluticasone and budesonide have higher affinities for the receptors.
- None has a clearly superior T.I.

INHALED CORTICOSTEROIDS

- Used prophylactically to control asthma, rather than to acutely reverse asthma symptoms.

INHALED STEROIDS - Therapeutic Uses

- Mild- moderate persistent asthma as well as those with severe disease (given once or twice daily improving compliance).

INHALED STEROIDS - Effects

- Control symptoms
- Improve quality of life
- Improve lung function
- Prevent exacerbations
- Reduce mortality
- Prevent irreversible airway changes
- Alter natural history of asthma (?)
INHALED CORTICOSTEROIDS

- With time, the dosage can sometimes be decreased, and some patients may be able to stop using the drug.

TOXICITY

- Recommended doses are free of serious toxicity. As dose is increased the likelihood of systemic adverse effects increase.

SALMETEROL/FLUTICASONE

- Combination inhalation device (alternative to increasing steroid dose).
- Long-term control of moderate to severe asthma.

BUDESONIDE/FORMOTEROL

- Approved in Europe, under study in the U.S.

TOXICITY

- Hoarseness, disturbed taste, cough and oral candidiasis can occur due to local deposition of the drug.

TOXICITY

- Suppression of hypothalamic-pituitary-adrenal axis can occur.
- Decreased bone density, cataract formation and with high doses, dermal thickening and glaucoma.
SYSTEMIC STEROIDS—
THERAPEUTIC USES

➤ Acute exacerbations of asthma unresponsive to bronchodilators (now even used in patients who respond to bronchodilators).

➤ Chronic severe asthma.

TOXICITY

➤ Chronic daily use can cause mood disturbances, glucose intolerance, weight gain, candidiasis, increased B.P., bone demineralization leading to osteoporosis, cataracts, immunosuppression and decreased linear growth in children.

TOXICITY

➤ Treatment for brief periods (5-10 days) causes little dose-related toxicity.

➤ Alternate day use can decrease incidence of adverse effects.

LEUKOTRIENE MODIFIERS

ROLE OF LEUKOTRIENES IN ASTHMA

➤ Cysteinyl leukotrienes are products of arachidonic acid metabolism (result from action of 5-lipoxygenase on arachidonic acid).
LEUKOTRIENES IN ASTHMA

- Antagonists block synthesis of leukotrienes (inhibition of 5-lipoxygenase) or act as competitive antagonists of the receptors.

PHARMACOKINETICS

- Rapidly absorbed upon oral administration.
- Extensively metabolized.

THERAPEUTIC USES

- Alternatives to inhaled steroids in patients with mild-persistent asthma.
- Add-on therapy in patients with mild to moderate persistent symptoms.
- Limited usefulness for acute attacks.

MONTELUKAST (Singulair)

- Leukotriene receptor antagonist, acts specifically on the LTD₄ receptor.
- Rapidly absorbed.
- Once daily treatment.
- Metabolized by CYP450 enzymes.

THERAPEUTIC USES

- Clinical trials have revealed considerable heterogeneity in response to therapy.
- “Responders and non responders”.

BIOSYNTHESIS OF LEUKOTRIENES, THEIR EFFECTS AND SITES OF THERAPEUTIC INTERVENTION
ZAFIRLUKAST (Accolate)
- A selective high affinity competitive antagonist at the cys-LT1 receptor.
- Twice daily treatment.

ZILEUTON (Zyflo)
- Potent and selective inhibitor of LT synthesis (5-LPO).
- Effective for maintenance treatment of asthma, but it must be taken four times a day and patients must be monitored for hepatic toxicity.

ADVERSE EFFECTS
- Mild headache, GI disturbances
- Elevation of liver enzymes (Zileuton).

OMALIZUMAB (Xolair)
- Recombinant humanized monoclonal antibody given SC that binds to IgE.

MECHANISM OF ACTION
- In many patients with asthma, an allergic component, mediated by antigen-specific IgE attached to receptors on mast cells and basophils, causes release of mediators that increase mucosal inflammation and airway smooth muscle spasm.
**MECHANISM OF ACTION**

- Omalizumab forms complexes with circulating free IgE and prevents it from binding to mast cells and basophils.

**PHARMACOKINETICS**

- Given as a single SC injection

**THERAPEUTIC USES**

- Used for patients with moderate to severe persistent asthma who have shown reactivity to an allergen and whose symptoms are not controlled by an inhaled steroid.

**ADVERSE EFFECTS**

- Injection site reactions are most common (redness, stinging etc).
- Increased tumor incidence.

**CROMOLYN AND NEDOCROMIL**

- Exact mechanism is unknown. Both work similarly.
- "Stabilize" mast cells and thus prevent release of mediators.
- Decrease airway hyperresponsiveness in some patients.
- No bronchodilating activity.
PHARMACOKINETICS

➢ Poor oral bioavailability so given as inhaled powder or aerosolized solution.

➢ Short duration of action (give at least 4 times a day).

THERAPEUTIC USES

➢ Used strictly as prophylactics (prevent attacks in mild to moderate asthma).

➢ No relief from acute attacks.

ADVERSE EFFECTS

➢ Minimal due to poor absorption from the airways.

➢ Some reflex wheezing that can be prevented with an inhaled β-agonist.

➢ Throat irritation, cough, mouth dryness.

➢ Bad taste.

THEOPHYLLINE

➢ Taken orally it stimulates relaxation of bronchial smooth muscles, but its mechanism is incompletely characterized.

➢ It should only be used where methods to measure theophylline blood levels are available.

THEOPHYLLINE

➢ Weak bronchodilator.

➢ Competitive antagonist at adenosine receptors.

➢ Phosphodiesterase inhibitor.

➢ Activation of histone deacetylases in the nucleus.
THERAPEUTIC USES

- Formerly widely used for maintenance therapy but largely replaced by safer drugs. Due to its modest benefits, narrow therapeutic window and required monitoring.
- Limited use in acute asthma.

THERAPEUTIC USES

- Adjunct for long term preventative therapy and for treatment of symptoms of chronic asthma (with steroids or $\beta_2$ agonists).
- Decreases the frequency and severity of symptoms in patients with persistent asthma, especially nocturnal asthma and can decrease steroid requirements.

ADVERSE REACTIONS

- Dose-dependent toxicity.
- Below 10 ug/ml few adverse effects.
- At conc’ns higher than 20 ug/ml nausea, nervousness, headache and insomnia may occur.

ADVERSE REACTIONS

- High conc’ns (>40 $\mu$g/ml) cause vomiting, hypokalemia, hyperglycemia, tachycardia, cardiac arrhythmias, tremor, neuromuscular irritability and seizures.

ADVERSE REACTIONS

- Many drugs and foods can increase or decrease serum theophylline concentrations as a result of competition for hepatic CYP450 drug-metabolizing enzymes.

ANTICHOLINERGIC AGENTS
**ANTICHLINERGICS**
- Parasympathetic pathways are important in bronchospasm in some asthmatics.
- Muscarinic M₃-receptor subtype is responsible for bronchial smooth muscle contraction.

**ANTICHLINERGICS**
- Competitively inhibit the effect of acetylcholine at muscarinic receptors (block all 5 subtypes but M₃ antagonism accounts for bronchodilating effect).

**IPRATROPIUM (Atrovent)**
- A selective quaternary amine derivative of atropine.
- Competitively inhibits muscarinic receptors (M₃ subtype)-blocks vagal stimulated bronchoconstriction and mucus secretion.
- Effect is slower and less intense than that of β₂ agonists.

**PHARMACOKINETICS**
- Inhalant.
- Poorly absorbed from the airway and does not readily enter the CNS.

**THERAPEUTIC USES**
- Useful in patients intolerant to β-agonists.
- Acute treatment of severe asthma ipratropium + short-acting β₂-agonist.
- COPD.
ADVERSE REACTIONS

- Poorly absorbed so few systemic effects.
- Dry mouth and pharyngeal irritation.
- Increases intraocular pressure in patients with glaucoma.