DRUG THERAPY FOR BRONCHIAL ASTHMA
Current Understanding of Asthma

- A chronic inflammatory disorder of the airway
- Infiltration of mast cells, eosinophils and lymphocytes
- Airway hyperresponsiveness
- Recurrent episodes of wheezing, coughing and shortness of breath
Commonest chronic disease in children & adults.

• Inflammatory condition in which there is recurrent reversible airways obstruction in response to irritant stimuli that are too weak to affect non-asthmatic subjects.

• Reversibility of airways obstruction in asthma contrasts with COPD, where obstruction is not reversible or incompletely reversible, by bronchodilators.
Control of Bronchial Tone

- **Autonomic Innervation**
  - Adrenergic stimulation
  - $\beta$: dilation
  - Cholinergic (muscarinic): constriction

- **Autocoids: released in asthmatic attack (Leukotrienes and Adenosine)**
  - produce bronchoconstriction
  - increase vascular permeability in bronchi and cause mucosal edema
Drug Treatment of Asthma

What is it? ‘A State of bronchial hyperreactivity resulting from a persistent inflammatory process in response to a number of stimuli in a genetically susceptible individual'

Key features of its pathophysiology
- mucosal oedema
- secretion of mucus
- epithelial damage
- bronchoconstriction

Therapy is thus aimed at
- Symptomatic relief - relieving bronchoconstriction
- Disease modification - reducing
Asthma: Pathological changes
Asthma Triggers

- Allergen exposure e.g. pet dander, pollens etc.
- Exercise/cold-air - drying airway mucosa.
- Drugs
- Food additives - tartrazines, sulphites
- Viral URTIs - especially rhinovirus.
Treatment Goals

- To reverse acute episodes
- To control recurrent episodes
- To reduce bronchial inflammation
Drugs Used in Asthma

Bronchodilators

• Beta-adrenergic agonists relax bronchial smooth muscle and decrease microvascular permeability
• Muscarinic antagonists inhibit the effects of endogenous ACh
• Theophylline reduce the frequency of recurrent bronchospasm
Drugs Used in Asthma (con’t.)

- Non-bronchodilators (for chronic use)
  - **Corticosteroids** control mucus production and edema
  - **Cromolyn** controls mediator release
  - **Leucotriene modulators** antagonize mediator receptors or decrease their synthesis
**β-ADRENERGIC AGONISTS**

- Given by inhalation to avoid systemic effects.
- are most effective bronchodilators.
- $\uparrow$ cyclic AMP in smooth muscle cells $\downarrow$ tone.
- Various drugs differ in their duration of action & receptor selectivity.
  - Short-acting (3-6 hr) & $\beta_2$ selective
    - Albuterol
  - Short acting & non-selective: Isoproterenol
  - Long-acting (>12 hr) & $\beta_2$ selective
    - Salmeterol
-ADRENERGIC AGONISTS, contd...

• Useful in prevention of exercise-induced asthma.

• Albuterol like drugs are useful in acute episodes of asthma.

• Prolonged acting Salmeterol used in maintenance treatment (prevent nocturnal attacks of asthma).

• Salmeterol has a slow onset of action & is not recommended for acute episodes of asthma.
- **β-ADRENERGIC AGONISTS contd....**

- **β**-adrenergic agonists have no anti-inflammatory activity.

- Their continuous use may result in desensitization of adrenergic receptors that can be prevented or reversed by corticosteroids.

- In high doses these drugs can produce **tachycardia, palpitations, and tremor**
**IPRATROPIUM**

- muscarinic receptor antagonist (a synthetic analog of atropine)
- given by inhalation negligible systemic effects
- longer duration of action than adrenergic agonists.
- **Used in COPD to decrease cholinergic tone**
- Used in asthma in combination with β-adrenergic agonists
- Combination more effective & less toxic than either drug alone
- Has no anti-inflammatory activity
Anti-Muscarinic Agents

- Competitively inhibits the effect of acetylcholine at muscarinic receptors effectively block the contraction of the airway smooth muscle and increase in secretion of mucus
- Ipratropium bromide - a quarternary ammonium derivative of atropine
- Delivered by inhalation
- Slightly less effective than beta agonist
- Effective in COPD
Methylxanthine drugs
a. caffeine
b. theophylline
c. theobromide

Mechanism of action
- inhibit the enzyme phosphodiesterase
  hydrolyses cyclic nucleotide result in high concentration of IC cAMP smooth muscle relaxation
- inhibition of cell surface receptors for adenosine
- anti-inflammatory effect: inhibit the late response of antigenic challenge.
PHARMACOLOGY OF METHYLXANTHINES

Theophylline

- stimulates respiratory center (CNS), increases sensitivity of respiratory center to pCO2
- relaxes smooth muscles of the bronchi,
- ineffective by aerosol, given orally
- effective bronchodilator & has slower onset of action than inhaled $\beta_2$-adren. Agonists.

- proposed mechanisms: adenosine receptor blockade; phosphodiesterase inhibition in high concentration.
Methylxanthines: Theophylline contd.

- Narrow safety index (10-20 ug/ml), its plasma concentration are to be monitored.
- Due to its high risk/benefit ratio, it is used as an second line or additional therapy.
- Clearance is influenced by smoking, and other drugs metabolized by liver.
- Toxicity is dependent on plasma concentration:
  - Mild (30 mg/L): nausea, vomiting, headache, insomnia, and nervousness
  - Potentially serious (40 mg/L): sinus tachycardia
  - Severe (45 mg/L): cardiac arrhythmias, seizures
Inhaled steroids

- Most widely used are beclamethasone & budesonide.
- Both are potent & absorbed from GIT and partial first-pass metabolism in liver
- When used up to 1000 µg –day no adrenocortical function effects
- Fluticasone propionate highly selective, poorly absorbed from GIT, subject to 100% first pass metabolism in liver. Safer in children
Pharmacokinetics of inhaled glucocorticoids

- Ninety percent swallowed (reduced by spacer or mouth rinsing)
- Ten percent deposited in lung
- Lung
  - First-pass inactivation in liver
  - Liver
  - Systemic side effects
- GI tract
  - Absorption from gut
INHALED CORTICOSTEROIDS

- decrease inflammation & edema in respiratory tract
- inhibit phospholipase A2 through synthesis of lipocortin,
- block release of arachidonic acid and its metabolites (leukotrienes)
- also inhibit production pro-inflammatory cytokines
- Used in chronic asthma, lowers the frequency of acute episodes
- are not bronchodilators & are not useful acute attacks
- May cause dysphonia and/or esophageal candidiasis
Side effects of inhaled steroids

- Depression of adrenocortical function
- Effects on bone metabolism
- Effects of growth in children
- Easy bruising & skin thinning
- Cataract formation
Phospholipid (from cell membrane)

Corticosteroids

Phospholipase A₂

Arachidonic acid

5-Lipoxygenase

Leukotrienes

Cyclooxygenase

PGE₂

PGF₂α

PGH₂

Prostacyclin (PGI₂)
SYSTEMIC CORTICOSTEROIDS (Prednisone)

- Oral (or injected) steroids are most effective drugs for asthma, unresponsive to bronchodilators and inhaled steroids.
- After recovery from severe exacerbation, oral corticosteroids are continued for 8 to 10 days.
- Alternate-day use decreases adverse effects.
- Potential adverse effects: glucose intolerance, sodium and water retention, increased BP, peptic ulcer, osteoporosis, cataract, immunosuppression, ACTH-suppression.
CROMOLYN SODIUM

- stabilizes mast cells & decreases airway responsiveness to spasmogens
- useful for prophylaxis only
- not effective in all patients
- more effective in children and adolescents than in older patients
- may take up to 4-6 weeks of its treatment to be effective in chronic asthma
- has no bronchodilating activity
- has virtually no toxicity
**MAST CELL SENSITIZATION**

First exposure to antigen causes the production of specific IgE antibodies, which attach to the surface of tissue mast cells and blood basophils. [Note: This attachment is inhibited by omalizumab.]

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**MAST CELL DEGRANULATION**

Subsequent exposure to antigen results in binding to surface-bound IgE molecules. The sensitized mast cells are stimulated to release granules containing histamine, leukotrienes, prostaglandins, and other potent chemical mediators.
Leukotriene Modulators:

Two types:

1. LT receptor antagonists: Montelukast, Zafirlukast)

2. Inhibitors of LT synthesis: inhibit 5-lipoxygenase, prevent conversion of arachidonic acid to leukotrienes: Zileuton

• Are not bronchodilators & not useful in acute episodes of asthma

• Reduce frequency of acute episodes
Leukotriene Modulators (cont’d)

- Less effective antiinflammatory agents than corticosteroids
- Used orally, useful in children in chronic treatment of mid to moderate asthma
- Generally well tolerated
- Zileuton can elevate liver enzymes
- Zileuton increase plasma concentrations of theophylline and warfarin because it inhibits cytochrome P450 enzymes in the liver.
Phospholipid (from cell membrane)

Corticosteroids

Phospholipase $A_2$

Arachidonic acid

5-Lipoxygenase

Leukotrienes

Cyclooxygenase

Prostaglandins

- $PGE_2$
- $PGF_{2\alpha}$

Prostacyclin ($PGI_2$)
Various severities of asthma

- Step-wise pharmacotherapy treatment program for varying severities of asthma
  - Mild Intermittent (Step 1)
  - Mild Persistent (Step 2)
  - Moderate Persistent (Step 3)
  - Severe Persistent (Step 4)
Mild Intermittent Asthma

- Day time symptoms ≤ 2 times a week
- Night time symptoms ≤ 2 times a month
- PEF or FEV1 ≥ 80% of predicted
  - PEF and FEV1 values are only for adults and for children over the age of 5

- No daily medication needed
- short-acting bronchodilator (albuterol) MDI as and when required
- Severe exacerbations may require systemic corticosteroids
Mild Persistent Asthma

- Day time symptoms > 2/week, but < 1/day
- Night time symptoms < 1 night / week
- PEF or FEV1 > 80% of predicted

**Step 2 (Mild persistent)**

- Preferred Treatment
  - Low-dose inhaled corticosteroid daily
- Alternative Treatment (no particular order)
  - Cromolyn
  - Leukotriene receptor antagonist
  - Nedocromil
  - Sustained release theophylline to maintain a blood level of 5-15 mcg/mL
Moderate Persistent Asthma

- Day time symptoms whole day
- Night time symptoms > 1 night / week
- PEF or FEV1 60%-80% of predicted

**Step 3 (Moderate persistent)**

- Preferred Treatment
  - Low-to-medium dose inhaled corticosteroids
  - WITH long-acting inhaled beta2-agonist

- Alternative Treatment
  - Increase inhaled corticosteroids within the medium dose range
  - Add leukotriene receptor antagonist or theophylline to the inhaled corticosteroid
Severe Persistent Asthma

- Day time symptoms: continual
- Night time symptoms: frequent
- PEF or FEV1 ≤ 60% of predicted

**Step 4 (Severe persistent)**

- Preferred Treatment
  - High-dose inhaled corticosteroids
  - AND long-acting inhaled beta2-agonists
  - AND (if needed) oral corticosteroids
Pharmacotherapy for Infants and Young Children (<5 years)

- Step 1 (mild intermittent)
  - No daily medication needed
Pharmacotherapy for Infants and Young Children (<5 years)

• Step 2 (mild persistent)
  • Preferred treatment
    • Low-dose inhaled corticosteroids
  • Alternative treatment
    • Cromolyn (nebulizer preferred)
    • OR leukotriene receptor antagonist
Pharmacotherapy for Infants and Young Children (<5 years)

- Step 3 (moderate persistent)
  - Preferred treatment
    - Low-dose inhaled corticosteroids and long-acting beta2-agonist
    - OR Medium-dose inhaled corticosteroids
  - Alternative treatment
    - Low-dose inhaled corticosteroids with either:
      - Leukotriene receptor antagonist
      - OR theophylline
Pharmacotherapy for Infants and Young Children (<5 years)

• Step 4 (severe persistent)
  • Preferred treatment
    • High-dose inhaled corticosteroids
    • AND long-acting inhaled beta2-agonist
    • AND (if needed) Oral corticosteroids
  • For young children, inhaled medications should be given by nebulizer, dry powder inhaler (DPI), or MDI with a chamber/spacer
Acute Exacerbations

- Inhaled albuterol is the treatment of choice in absence of impending respiratory failure
- MDI with spacer as effective as nebulizer with equivalent doses
- Adding an antibiotic during an acute exacerbation is not recommended in the absence of evidence of an acute bacterial infection
Exercise-induced Bronchospasm

- Short acting Beta Agonist are best pre-treatment
<table>
<thead>
<tr>
<th>ASTHMA SEVERITY</th>
<th>SYMPTOM FREQUENCY</th>
<th>MEDICATIONS</th>
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<tbody>
<tr>
<td>Mild intermittent</td>
<td>&lt;2 days/week,</td>
<td>None; course of systemic glucocorticoids for occasional, severe exacerbations</td>
</tr>
<tr>
<td></td>
<td>&lt;2 nights/month</td>
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<tr>
<td>Mild persistent</td>
<td>&gt;2 per week but</td>
<td>Low-dose inhaled glucocorticoids.</td>
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<td></td>
<td>&lt; once per day</td>
<td>Alternate: cromolyn, nedocromil, leukotriene modifier, or sustained release theophylline</td>
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<tr>
<td></td>
<td>&gt;2 nights/month</td>
<td></td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>Daily,</td>
<td>Low- to medium-dose glucocorticoids and long-acting inhaled $\beta_2$-agonists.</td>
</tr>
<tr>
<td></td>
<td>&gt;1 night/week</td>
<td>Alternate: leukotriene modifier or theophylline</td>
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<tr>
<td>Severe persistent</td>
<td>Continual during day, frequent at night</td>
<td>High-dose glucocorticoids and long-acting inhaled $\beta_2$-agonist and (if needed) systemic glucocorticoids</td>
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ACUTE SEVERE ASTHMA (STATUS ASTHMATICUS)

This is a life-threatening emergency

recommendations of the British Thoracic Society
Immediate treatment

✓ Oxygen by mask (humidified, to help liquefy mucus).
✓ Salbutamol by nebuliser in a dose of 2.5-5 mg over about 3 min, repeated in 15 min.
✓ Terbutaline 5-10 mg is an alternative.
✓ Prednisolone 30-60 mg p.o. or hydrocortisone 200 mg i.v.
✓ Avoid sedation of any kind.
✓ Chest x-ray to exclude pneumothorax
If life-threatening features are present (absent breath sounds, cyanosis, bradycardia, exhausted appearance or PEFR < 30% predicted.

- *Ipratropium 0.5 mg should be added to the nebulised B2-agonist.*

- Give i.v. either *salbutamol 250 microgram over 10 minutes* (as nebulised salbutamol may not be reaching the distal airways) or *aminophylline 5 mg/kg.*

- *Aminophylline should not be given to patients already taking oral theophyllines.*

- Alert the intensive care unit
Subsequent management

If the patient is improving,

- continue: 40-60% oxygen
- Prednisolone 30-60 mg daily or hydrocortisone 200 mg 6-hourly
- Nebulised salbutamol or terbutaline 4-hourly.
If the patient is not improving after 15-30 minutes:

- Continue oxygen and glucocorticoid
- Give nebulised (B2-adrenoceptor agonist more frequently, up to every 15-30 minutes
- Add ipratropium 0.5 mg to nebuliser and repeat 6-hourly until patient is improving.
If the patient is still not improving give:

- i.v. infusion of [B2-adrenoceptor agonist or aminophylline (0.9 microgram/kg/min)]
- i.v. infusion of a (B2-adrenoceptor agonist (as above) as an alternative
- Contact the intensive care unit to discuss intubation and mechanical ventilation.
• Monitoring response to treatment
• By peak expiratory flow rate (PEFR) every 15-30 minutes
• Oxygen saturation: maintain > 92%
Drugs which predispose to asthma

BETA BLOCKERS

NSAIDS esp aspirin