S. B. K. S. Medical Institute & Research Center

Subject: Pharmacology

Topic: Pharmacotherapy of Bronchial Asthma: Session II

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Disorders of Respiratory Function

1. Bronchial asthma

2. Cough

3. Allergic rhinitis

4. Chronic obstructive pulmonary disease

(COPD, also called emphysema)

Drugs Used In The Prevention Of Acute Attacks (Maintenance Therapy)

(1) Inhaled long acting β-agonists (LABA) e.g. salmeterol, formoterol.

(2) Inhaled glucocorticoids

(3) Oral theophylline and

(4) Oral leukotriene modifiers

Drug therapy
Two drug categories are used:

Anti-inflammatory drugs (basic)

Are divided into:

- **hormone-containing (Corticosteroids)**
- **Non-hormone-containing (Cromones, Leukotriene receptor antagonists)**

Bronchodilators

Three groups:

- **Beta 2-agonists**
- **Anticholinergic Drugs**
- **Methylxanthines**

Mast cell stabilisers Cromolyn sodium/ Sodium cromoglycate, and Nedocromil

- Mast cell stabilisers. stabilize cell membranes
- used mainly in pediatric practice (in childhood)
- in case of intermittent or mild persistent asthma.

Leukotriene receptor antagonists (Montelukast, Zafirlukast)

- have the moderate anti-inflammatory activity
- used in case of aspirin-induced asthma and asthma of physical exertion.

Bronchodilators

Beta 2-agonists

Stimulates Beta 2-adrenergic receptors of bronchi

Anticholinergic drugs

reduce tonus of vagus

SMOOTH MUSCLE RELAXATION

Methylxanthines

inhibit phosphodiesterase

Drug Therapy During an Acute Attack

Selective short acting β2 adrenergic receptor agonists (SABA)

- Relax the smooth muscle of all airways.
- Enhance mucociliary clearance from the respiratory tract.
- Suppress microvascular leakage in the airway.
- Inhibit mediator release from the mast cells and the basophils, and cytokine release from the inflammatory cells in the airway.
- May inhibit release of acetylcholine.

EXAMPLES OF SABA :

- Salbutamol, Levosalbutamol
- Terbutaline, fenoterol, bitolterol, pirbuterol, tolubuterol and rimiterol
- FENOTEROL has been associated with greater cardiac toxicity in patients with acute asthma.

USES OF SABA - VERY EFFECTIVE FOR:

(1) Treating acute attacks and

(2) Prevention of exercise-induced asthma.

- **Inhaled Beta 2-agonists are the basic drug group among bronchodilators.**

  - Short-acting (duration of action 5-6 h) b2-agonists - salbutamol, fenoterol - are used for quick relief of asthma symptoms.
  - Long-acting (> 12 h) b2-agonists - salmoterol, farmoterol - for prevention of asthma symptoms occurring.

Adverse effects

- Skeletal muscle tremors, vasodilation, tachycardia, hyperglycemia, hypokalemia, hypomagnesemia.

- These are minimal when the drugs are given by inhalation.

ANTICHOLINERGICS:

Ipratropium Bromide, Oxitropium, Tiotropium

- Preferred drug in patients with COPD.
- It is particularly useful in patients with concomitant heart disease and those intolerant to β agonists.
- Used predominantly in night-time asthma and in elderly patients because of the least cardiotoxic effect.

•A combination of ipratropium and a beta adrenergic agonist by inhalation produces additive effects because ipratropium acts on large and medium sized bronchi; whereas β2 agonist act on the smaller bronchi.

•It is also useful in asthmatic attack induced by β–blockers.

Anti-cholinergic drugs

- Uses :
  - COPD
  - Bronchial asthma as an adjuvant to β2 agents
- Oxytropium :
  - Is related to ipratropium and is given twice a day as aerosol.
- Tiotropium :
  - is a longer acting drug with a duration of action of 24 hrs.

XANTHINE DERIVATIVES

- Naturally occuring : methylxanthines
  - Caffeine, theophylline, theobromine.
- Of them, theophylline is the most effective compound in producing relaxation of the bronchial muscle.
- Theophylline & its related compounds :
  - Aminophylline, choline theophyllinate, etophylline.

- Theophylline and its compounds have been extensively used in asthma, but are not considered first line drugs any more. They are used more often in COPD.
- Methylxanthines in comparison with other bronchodilators have the less bronchodilating potential.
- There are long-acting (>12 h) - Doxophylline A long-acting oral methylxanthine & short-acting (aminophylline, theophylline) drugs in this group.

Theophylline

- Mechanism of action (MOA) :
  - It inhibits the enzyme phosphodiesterase (PDE) and thus prevents degradation of cAMP to 5 AMP.
- This increases the intracellular cAMP production resulting in
  - Relaxation of plain muscle
  - Cardiac stimulation
  - Inhibition of activation of inflammatory cells.
  - Inhibits adenosine receptors on the cell surface.

Theophylline

- Therapeutic uses :
  - Acute attack of Bronchial asthma
    - Aminophylline (250-500 mg) slow i.v infusion, it acts rapidly in severe attacks.
  - Prophylaxis of mild to moderate bronchospasm
  - COPD with CCF
  - Apnea of preterm infants.
- Sustained release preparations are available which produce blood levels for 12 hours

AMINOPHYLLINE:

Therapeutic uses:

1) Acute attack of asthma:

- If treatment with inhaled selective SABA in adequate doses fails to relieve an acute attack in about half to one hour, aminophylline is administered by IV infusion in 5% glucose in a dose of 5 mg/kg over 15-30 minutes, followed by 0.5-1 mg/kg per hour for several hours.
- The infusion rate should be lowered in patients with cirrhosis, pneumonia, acute viral infection and congestive heart failure and in patients receiving drugs which interfere with its metabolic degradation.

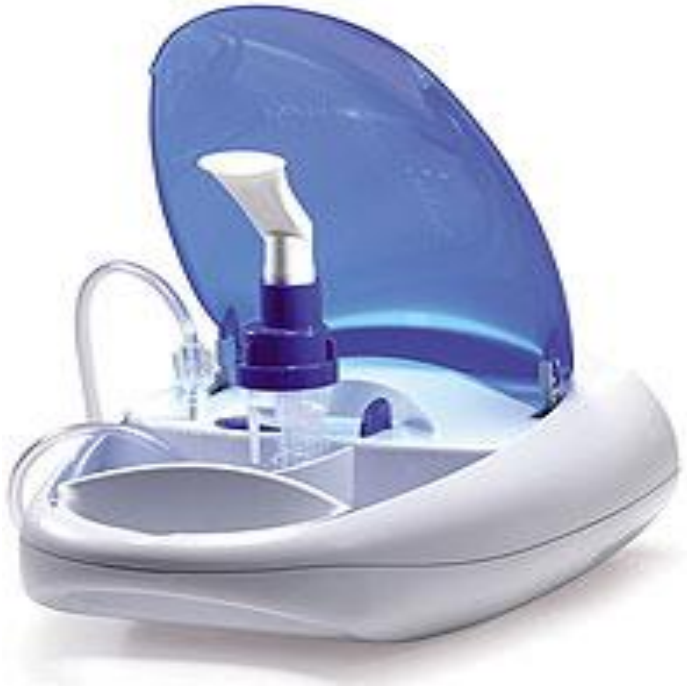
2) Chronic persistent asthma:

- Slow release oral preparations may be useful in patients with persistent bronchospasm between acute attacks and in preventing nocturnal attacks.
- However, these preparations may also prolong the toxic effects as peak plasma level is reached 12-24 hours after the ingestion.
- **NOTE**: If an acute asthmatic attack is not terminated within 2 hours by the above measures, the patient should be treated as a case of severe acute asthma (status asthmaticus).

Adverse reactions

- Gastric irritation, anorexia, nausea, vomiting, abdominal discomfort, headache, tremor, anxiety, nervousness, tachycardia and insomnia, cardiac arrhythmias and convulsions.

Combined inhaled drugs (corticosteroids with b2-agonists) – with use of delivery devices (nebulisers, spacers, spinhalers) enhance the effectiveness of asthma therapy.



Leukotriene (LT) modifiers:

(a) LT receptor antagonists: Montelukast; Zafirlukast.

(b) LT synthesis inhibitors: Zileuton.

(a) **Montelukast and Zafirlukast -** Both have similar actions and clinical utility. They competitively antagonize cysLT1 receptor mediated bronchoconstriction, increased vascular permeability and recruitment of eosinophils.

Montelukast and zafirlukast

- **Montelukast** and **zafirlukast** are **indicated** for

prophylactic therapy of mild-to-moderate asthma as alternatives to inhaled glucocorticoids.

- Are very safe drugs; produce **few side effects** like headache and rashes. Eosinophilia and neuropathy are infrequent. Few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) have been reported.

ZILEUTON:

- It is a 5-LOX inhibitor, blocks LTC4/D4 as well as LTB4 synthesis. It therefore has the potential to prevent all LT induced responses including those exerted by activation of cysLT1 receptor.
- However, clinical efficacy in asthma is similar to montelukast.
- The duration of action of zileuton is short and it has **hepatotoxic potential**. These limitations have **restricted its use**.

MAST CELL STABILIZERS

- **Sodium cromoglycate (Cromolyn sodium)**
- Synthetic chromone derivative which inhibits degranulation of mast cells (as well as other inflammatory cells) by trigger stimuli.
- Release of mediators of asthma like histamine, LTs, PAF, interleukins, etc. is restricted.
- It is also not a bronchodilator and does not antagonize constrictor action of histamine, ACh, LTs, etc.
- Therefore, it is **ineffective** if given during an asthmatic attack.

USES

1. **Bronchial asthma**: Sod. cromoglycate is used as a long-term prophylactic in mild-to-moderate asthma.
2. **Allergic rhinitis**: Not a nasal decongestant, but regular 4 times daily prophylactic use as a nasal spray produces symptomatic improvement in many patients after 4–6 weeks: need for nasal decongestants is reduced.
3. **Allergic conjunctivitis**: Regular use as eye drops is beneficial in some chronic cases.

Antihistaminics & Mast Cell Stabilisers

KETOTIFEN: PAF antagonists & H1 receptor blocker, is claimed to be useful in asthma. It is believed to inhibit airway inflammation induced by platelet activating factor (PAF) in primates. It can cause drowsiness. Its usefulness in asthma is equivocal.

- Mast cell stabilisers such as **cromolyn sodium** 4%, **ketotifen** 0.025%, **nedocromil** 2% and **epinastin** 0.05% can also be used to treat allergic and vernal conjunctivitis.

ANTI-IgE ANTIBODY

<u>Omalizumab:</u> It is a humanized monoclonal antibody against IgE.

Administered s.c., it neutralizes free IgE in circulation without activating mast cells and other inflammatory cells.

On antigen challenge, little IgE is available bound to the mast cell surface receptors (FcεR1) to trigger mediator release & cause bronchoconstriction.

- In severe extrinsic asthma, omalizumab has been found to reduce exacerbations and steroid requirement.

- No benefit has been noted in nonallergic asthma.

- It is very expensive; use is reserved for resistant asthma patients with positive skin tests or raised IgE levels who require frequent hospitalization.

- It is being tried in other allergic diseases as well.

CHOICE OF TREATMENT

(K. D. Tripathi Textbook)

A stepwise guideline to the treatment of asthma as per needs of the patient has been recommended:

1. **Mild episodic asthma**: (symptoms less than once daily, normal in between attacks): Inhaled short-acting β2 agonist at onset of each episode. No regular prophylactic therapy (Step-1).
2. **Seasonal asthma**: Start regular inhaled cromoglycate/low-dose inhaled steroid (200-400 μg/day) 3-4 weeks before anticipated seasonal attacks and continue till 3-4 weeks after the season is over. Treat individual episodes with inhaled short-acting β2 agonist.

3. **Mild chronic asthma with occasional exacerbations:** (symptoms once daily or so) Regular inhaled low-dose steroid (Step-2). Alternatively, inhaled cromoglycate. Episode treatment with inhaled short-acting β2 agonist.

4. **Moderate asthma with frequent exacerbations** (attacks affect activity, occur > 1 per day or mild baseline symptoms) Increasing doses of inhaled steroid (up to 800 μg/day) + inhaled long-acting β2 agonist (Step-3).

Leukotriene antagonists may be tried in patients not accepting inhaled steroids and in those not well controlled.
Theophylline may be used as alternative additional drug. Episode treatment with inhaled short-acting β2 agonist.

5. **Severe asthma (continuous symptoms; activity limitation; frequent exacerbations/hospitalization):** Regular high dose inhaled steroid (800-2000 μg/day) through a large volume spacer device + inhaled long-acting β2 agonist (salmeterol) twice daily.

Additional treatment with one or more of the following (Step-4):

Leukotriene antagonist/sustained release oral theophylline/oral β2 agonist/inhaled ipratropium bromide.

Rescue treatment with short-acting inhaled β2 agonist.

In patients not adequately controlled or those needing frequent emergency care-institute oral steroid therapy (Step-5).

Attempt withdrawing oral steroid periodically.

STATUS ASTHMATICUS

• **Severe acute asthma (Status asthmaticus)** is a serious medical emergency, requiring urgent hospitalisation and vigorous therapy.

• It is often precipitated by:

1. An acute respiratory infection.
2. Abrupt cessation of glucocorticoid therapy.
3. Drugs (aspirin or NSAID) or inhaled allergens; or
4. Acute emotional stress.

Status Asthmaticus is a life threatening form of asthma **defined** as “a condition in which a progressively worsening attack is unresponsive to the usual appropriate therapy with adrenergic drugs and that leads to pulmonary insufficiency.

- History: Previous history of wheezing, known asthmatic, non Compliant Previous hospitalizations or intubations history.

- Presence of hypoxia, bilateral wheeze or silent chest and mental confusion with impending collapse.

- CBC : elevation in WBC may indicate infection specially bacterial ,signs of viral infection such as leucopenia and thrombocytopenia.

- ABG might help in the presence of normal or elevated CO2 that indicate severe presentation.

- Chest x-ray to exclude reversible pathology such as pneumothorax.

MANAGEMENT

- If the patient does not respond to appropriate therapy in the emergency department, if the frequency of required aerosol treatments is greater than can be administered on the ward, or if the patient is deteriorating significantly despite appropriate therapy, he/she should be transferred/admitted to the ICU.
- **Oxygen therapy should be started immediately to correct hypoxemia.**

• Any patient of asthma has the potential to develop acute severe asthma which may be life-threatening.

•Upper respiratory tract infection is the most common precipitant.

(i) Hydrocortisone hemisuccinate 100 mg (or equivalent dose of another glucocorticoid) i.v. stat, followed by 100-200 mg 4-8 hourly infusion; may take upto 6 hours to act.

(ii) Nebulized salbutamol (2.5–5 mg) + ipratropium bromide (0.5 mg) intermittent inhalations driven by O2.

(iii) High flow humidified oxygen inhalation.

(iv) Salbutamol/terbutaline 0.4 mg i.m./s.c. may be added, since inhaled drug may not reach smaller bronchi due to severe narrowing/plugging.

(v) Intubation and mechanical ventilation, if needed.

(vi) Treat chest infection with intensive antibiotic therapy.

(vii) Correct dehydration and acidosis with saline + sod. bicarbonate/lactate infusion

- **Magnesium sulfate Intravenous** magnesium sulfate 2 gm infused over 20 min has **bronchodilator activity** in acute asthma, possibly due to inhibition of calcium influx into airway smooth muscle cells.

Prophylaxis

Preservation of the environment, healthy life-style (smoking cessation, physical training) – are the basis of primary asthma prophylaxis. These measures in combination with adequate drug therapy are effective for secondary prophylaxis.

Chronic Obstructive Pulmonary Disease

Chronic Obstructive Pulmonary Disease

- COPD is characterized by airflow limitation caused by chronic bronchitis or emphysema often associated with long term tobacco smoking.

- This is usually a slowly progressive and largely irreversible process, which consists of increased resistance to airflow, loss of elastic recoil, decreased expiratory flow rate, and overinflation of the lung.

- COPD is clinically defined by a low FEV1 value that fails to respond acutely to bronchodilators, a characteristic that differentiates it from asthma.

• **Chronic Obstructive Pulmonary Disease (COPD)** is characterized by “air flow resistance that is not reversible”. It includes:

(1) **Emphysema** an anatomically defined entity associated with enlarged and distorted lung alveoli, and

(2) **Chronic bronchitis**, a clinical entity associated with disease of small brochioles with chronic airflow obstruction, chronic cough and marked expectoration.

• **Chronic bronchitis without airflow obstruction is not COPD**.

CURRENT THERAPY OF COPD

- **Inhaled bronchodilators**
- **Inhaled glucocorticoids**
- **Oxygen inhalation**
- **Prophylactic antibiotics**
- **Preventation of dehydration; and**
- **Physiotherapy, pulmonary rehabilitation and education.**

MCQs

Q. 1. The following is the example of sympathomimetic bronchodilator:

a) Beclomethasone

b) Budesonide

c) Salbutamol

d) Flunisolide

Q. 2. The following Leukotriene (LT) modifiers has restricted use due to hepatotoxic potential:

a) **Zafirlukast**

b) **Montelukast**

c) **Zileuton**

d) **None of the above**

Q. 3. The following is the example of mast cell stabilizer:

a) **Zileuton**
b) **Budesonide**
c) **Beclomethasone**
d) **Disodium cromoglycate**

Q. 4. The following is the example of methylxanthines:

a) **Ketotifen.**
b) **Budesonide**
c) **Beclomethasone**
d) **Doxophylline.**

Q. 5. The following anticholinergic has longer duration of action:

a) Ipratropium Bromide

b) Oxitropium

c) Tiotropium

d) All of the above

REFERENCE TEXT BOOKS

- **K. D. Tripathi M.D., Essentials of Medical Pharmacology.**

- **Satoskar & Bhandarkar, Pharmacology and Pharmacotherapeutics.**