

# DRUGS FOR BRONCHIAL ASTHMA

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*[BOTH PUBLISHED BY JAYPEE BROTHERS MEDICAL PUBLISHERS, INDIA]*

# DRUGS FOR BRONCHIAL ASTHMA

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- APPROACHES TO TREATMENT
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## DEFINITION

- Bronchial asthma is characterized by hyper-responsiveness of tracheobronchial smooth muscle to a variety of stimuli.
- This results in narrowing of air tubes.
- This is often accompanied by increased secretion, mucosal edema and mucus plugging.

# SYMPTOMS

- Dyspnoea
- Wheezing
- Cough
- Limitation of activity

# PREDISPOSING FACTORS

- Allergy
- Infection
- Pollutants
- Exercise
- Exposure to cold air
- Psychogenic problems

## TYPES

- There are mainly two types of bronchial asthma:
  1. Extrinsic asthma: Episodic, less prone to status asthmaticus.
  2. Intrinsic asthma: Perennial, more prone to status asthmaticus.

## MECHANISM OF ASTHMA

- Due to the predisposing factors, in the site of asthma, there are recruitment of two types of cells. They are:
  1. Mast cells
  2. Other inflammatory cells
- These cells secrete a variety of mediators:
  1. Stored in granules: Histamines, Proteases, TNF- $\alpha$
  2. From cell membrane: PGs, LTs, PAF
  3. Specific proteins: Interleukins, TNF- $\alpha$

- The mediators together causes the following:
  1. Constrict bronchial smooth muscle
  2. Cause mucosal edema
  3. Hyperemia
  4. Produce viscid secretion
- All these results in reversible airway obstruction.



## APPROACHES TO TREATMENT

- Prevention of antigen-antibody reaction
- Neutralization of IgE
- Suppression of inflammation and bronchial hyperactivity
- Prevention of release of mediators
- Antagonism of released mediators
- Blockade of constrictor neurotransmitter
- Sympathomimetics
- Directly acting bronchodilators

# CLASSIFICATION OF DRUGS APPLIED

- Bronchodilators:
  1.  $\beta$ 2 Sympathomimetics
  2. Methyl-xanthines
  3. Anticholinergic
- Leukotriene antagonists
- Mast cell stabilizers
- Corticosteroids
- Anti-IgE antibody

DRUGS

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# SYMPATHOMIMETICS

- Mechanism of action:
  - Adrenergic drugs
    - Work through  $\beta_2$  receptor stimulation
  - Increased level of c-AMP in bronchial smooth muscle cells
    - Bronchial smooth muscle relaxation
- Conditions where these drugs should not be used:
  1. Hypertensives
  2. Ischaemic heart diseases
  3. Patients being treated with Digitalis

# SALBUTAMOL

- It is a highly selective  $\beta_2$  agonist.
- It can be administered in two routes:
  1. Inhalation route
  2. Oral route
- Inhaled salbutamol produces bronchodilation within 5 minutes and action lasts for 2-4 hours. So it is used to prevent terminate attacks of asthma.
- Orally taken salbutamol's bioavailability is 50% due to its digestion in the gut wall. Its action lasts for 4-6 hours.

# SALBUTAMOL

- The side effects are:
  1. Palpitation
  2. Restlessness
  3. Throat irritation
  4. Ankle edema

## DOSAGE:

2-4 mg oral, .25-.50 mg i,m/s.c, 100-200 microgram by inhalation.

## TERBULATINE

- It is similar to salbutamol in properties and use.
- Dosage: 5 mg oral, .25 mg s.c, 250 microgram inhalation.

Effect of regular use of salbutamol and terbutaline:

1. Regular use of these two drugs may increase bronchial hyper responsiveness.
2. Regular use also downregulates bronchial  $\beta_2$  receptors.
3. So it is advised to patients that patients requiring regular medication should be treated with inhaled steroids.

# OTHER SYMPATHOMIMETIC DRUGS

DRUGS	SOURCE/ NATURE	MECHANISM OF ACTION	SIDE EFFECTS	DOSAGE
Bambuterol	Bis-carbamate ester	The drug is slowly hydrolyzed in plasma and lungs by pseudo-cholinesterase.		Single evening dose: 10-20 mg.
Salmeterol	It is a long acting selective $\beta_2$ agonist with slow onset of action.		Long use may worsen the condition of asthma.	It is advised that long acting $\beta_2$ agonists should be used with an inhaled steroid.
Formoterol	Another long acting $\beta_2$ agonist with faster onset of action	It can act for 12 hours after inhalation.		12-24 microgram inhalation twice daily
Ephedrine	It has $\alpha + \beta_1 + \beta_2$ actions.	Causes mild slowly development of bronchodilation for 3-5 hours.	Low efficacy Frequent side effects	It is not used now.



# METHYL XANTHINES

- DRUGS
- MECHANISM OF ACTION
- PHARMALOGICAL ACTIONS
- MAIN DRUG: THEOPHYLLINE

## METHYL XANTHINES: DRUGS

- The main compounds in methyl xanthine family are theophylline and its compounds.
- But they are not used as the first line drug in treatment of asthma.
- They are primarily used in the treatment of COPD.
- All these compounds are derived from plant sources as:
  1. Caffeine
  2. Theophylline
  3. Theobromine

# MECHANISM OF ACTION

- There are three distinct mechanisms of action of methyl xanthine compounds:
- Release of  $Ca^{++}$  from sarcoplasmic reticulum.
- Inhibition of PDE (Phosphodiesterase): So produces intracellular degradation of ATP and increased production of c-AMP. So following functions occur:
  1. Bronchodilation
  2. Cardiac stimulation
  3. Vasodilation
- Blockade of adenosine receptors: Increased intracellular level of adenosine in CVS and CNS and smooth muscle cells causing:
  1. Bronchodilation
  2. Cerebral artery dilation
  3. Cardiac pacemaker inhibition
  4. Gastric secretion inhibition

# PHARMACOLOGICAL ACTIONS: METHYL XANTHINES

1. CNS
2. CVS
3. Smooth muscles
4. Kidney
5. Skeletal muscle
6. Stomach
7. Mast cells and inflammatory cells
8. Metabolism

# PHARMACOLOGICAL ACTIONS (PART 1)

## EFFECT ON CNS:

- Methyl xanthines are primarily CNS stimulants.
- Caffeine works better than theophylline.
- The main functions are:
  1. Sense of well being
  2. Alertness
  3. Improve performance
  4. Increase motor activity
  5. Stimulation of respiratory, vagal and vasomotor centres.

## EFFECTS ON CVS:

1. Dilation of systemic blood vessels. (Theophylline)
2. Constriction of cerebral blood vessels. (Caffeine)
3. Its effect on BP is variable and unpredictable.
4. Directly stimulate the heart.
5. Increases the force of contraction.
6. It increases cardiac output and cardiac work.
7. It has dual role on heart rate:
  - It increases heart rate by direct action. Example: Theophylline.
  - At the same time decreases it by vagal stimulation. Example: Caffeine.

## PHARMACOLOGICAL ACTIONS (PART 2)

### SMOOTH MUSCLES:

1. All smooth muscles are relaxed. Most prominent effect is on bronchi.
2. Bronchodilation produced is slow and sustained.
3. Vital capacity is increased.
4. Biliary spasm is relieved.

\* Theophylline is more potent than caffeine in this action.

### KIDNEY:

1. Methyl xanthines are mild diuretics.
2. They act by inhibiting reabsorption of  $\text{Na}^+$  and water.
3. Additional effects are increased blood flow and GFR.

\*Theophylline is more potent than caffeine in this action.

## PHARMACOLOGICAL ACTIONS (PART 3)

### SKELETAL MUSCLE:

1. It is primarily the action of caffeine.
2. High conc. of caffeine increases release of  $\text{Ca}^{++}$  from sarcoplasmic reticulum, which increases the contractile power of skeletal muscle.
3. It increases neuromuscular transmission by increasing Ach release, which increases muscular work.

### STOMACH:

1. Methyl xanthines increase secretion of HCl and pepsin in stomach.
2. They are also gastric irritants.

## PHARMACOLOGICAL ACTIONS (PART 4)

### MAST CELLS AND INFLAMMATORY CELLS:

1. The main effect is by Theophylline.
2. The main effect is inhibition of inflammatory responses.
3. Theophylline decreases release of Histamine and other inflammatory mediators from the above mentioned cells.

### METABOLISM:

1. The main effect is by caffeine.
2. The effects are:
  - Increased BMR.
  - Increased plasma FFA level.



# MAIN DRUG: THEOPHYLLINE

1. PHARMACOKINETICS
2. USES
3. ADVERSE EFFECTS
4. INTERACTIONS
5. DOSAGE

# PHARMACOKINETICS OF THEOPHYLLINE

- This drug is well absorbed orally.
- It is distributed in all tissues. It also crosses the placenta and secreted as milk.
- The volume of distribution= .5 litre/ kg
- The plasma protein bound form= 50% and free form= 50%.
- There is extensive demethylation and oxidation of the drug in the liver.
- Only 10% of drug is excreted unchanged in urine.
- Plasma half life= 7-12 hours. In children= 24-36 hours.
- Plasma half life is prolonged with higher dose as the kinetics changes from 1<sup>st</sup> order to zero order reaction.

## USES OF THEOPHYLLINE

1. Bronchial asthma: Because of limited efficacy and safety, its use has declined. Oral theophylline is used in severe asthma, as 3<sup>rd</sup> line drug.
2. COPD (Chronic obstructive pulmonary disease): It is highly useful in preventing COPD.
3. Apnoea in premature infant: Theophylline reduces the frequency and duration of Apnoea.

## ADVERSE EFFECTS OF THEOPHYLLINE

1. Theophylline has a narrow margin of safety.
2. Toxicity starts from upper part of therapeutic concentration.
3. Primary effect is on CVS, CNS and GIT.
4. There is highly irritant effect of theophylline such as:
  - Gastric pain (with oral administration)
  - Rectal inflammation (with suppositories)
  - Pain at the site of i.m injection
  - Rapid i.v may cause precordial pain, syncope and even sudden death.

# INTERACTIONS OF THEOPHYLLINE

1. Agents which induce its metabolism decreases its plasma level:

- a) Smoking
- b) Phenytoin
- c) Rifampicin
- d) Phenobarbitone.

2. Agents which inhibit its metabolism increases its plasma level:

- a) Erythromycin
- b) Ciprofloxacin
- c) Cimetidine
- d) Oral contraceptive
- e) Allopurinol

# INTERACTIONS OF THEOPHYLLINE

3. Theophylline increases the effect of some drugs:

- a) Sympathomimetics
- b) Oral anticoagulants
- c) Digitalis
- d) Hypoglycaemics

4. Theophylline decreases the effect of some drugs:

- a) Phenytoin
- b) Lithium

## DOSAGE

- Theophylline is less soluble in water. So some soluble complexes and salts have been prepared for parenteral use.

# ANTICHOLINERGICS

1. DRUGS
2. USES
3. MECHANISM OF ACTION
4. DOSAGE



# DRUGS

- The main anticholinergic drugs used in bronchial asthma are: Ipratropium and Tiotropium.

## MECHANISM OF ACTION

- The drugs produce bronchodilation by blocking cholinergic constrictor tone.
- The drugs act primarily on the large airways.
- Combination of ipratropium with a  $\beta_2$  agonist causes more marked and long lasting bronchodilation.

# USES

- Anticholinergic drugs are mainly used in treatment of:
  1. Asthmatic bronchitis
  2. COPD Patients
  3. Psychogenic asthma

## DOSAGE

- Duolin = Salbutamol + Ipratropium
- Duolin inhaler- (100 + 20) microgram per metered dose.
- Duolin rotacap- (200 + 40) microgram per rotacap.
- Duolin respules- (2.5 mg + 500 microgram) in 2.5 ml solution.

# LEUKOTRIENE ANTAGONISTS

- DRUGS
- PHARMACOKINETICS
- MECHANISM OF ACTION
- SIDE EFFECTS
- DOSAGE

## LEUKOTRIENE ANTAGONISTS: DRUGS

- There are mainly two leukotriene antagonist drugs. They are:
  1. Montelukast
  2. Zafirlukast
- Both these two drugs are within the chemical family of Cysteinyl Leukotrienes antagonists.

# LEUKOTRIENE ANTAGONISTS: PHARMACOKINETICS

- Both the drugs are well absorbed orally.
- They bound with plasma very highly, so the volume of distribution is very low.
- They are extensively metabolized by CYP2C9 and CYP3A4 isoenzymes in liver.
- Plasma half life: Montelukast: 3-6 hours.  
Zafirlukast: 8-12 hours.

# LEUKOTRIENE ANTAGONISTS: MECHANISM OF ACTION

- Both the drugs Montelukast and Zafirlukast act similarly.
- They competitively inhibit cysteinyl leukotriene receptors and causes:
  1. Bronchodilation
  2. Suppression of bronchial inflammation
  3. Reduced sputum eosinophil count
- They are used for prophylactic therapy of mild to moderate asthma as alternatives of inhaled glucocorticoids.
- In severe asthma they may be used to reduce dosage of steroids.
- They are not to be used for terminating episodes of asthmatic attack.
- They are effective in treatment of aspirin induced asthma.



## LEUKOTRIENE ANTAGONISTS: SIDE EFFECTS

- Montelukast and zafirlukast are very safe drugs.
- They produce very few side effects like headache and rashes.
- Very few cases of Churg-Strauss syndrome (vasculitis with eosinophilia) has been reported.

## LEUKOTRIENE ANTAGONISTS: DOSAGE

- Montelukast: 10 mg OD.
- Zuvair: 10 mg, 20 mg TABLETS.

# MAST CELL STABILIZERS

- DRUGS
- PHARMACOKINETICS
- MECHANISM OF ACTION
- USES
- ADVERSE EFFECTS
- DOSAGE

## MAST CELL STABILIZERS: DRUGS

- Sodium cromoglycate
- Kitotifen

# MAST CELL STABILIZERS: PHARMACOKINETICS

## 1. Sodium cromoglycate:

- Sodium cromoglycate is not absorbed orally.
- It is absorbed as an aerosol through metered dose inhaler.
- Only a small fraction is absorbed systemically.
- Rest of the portion is rapidly excreted unchanged in urine and bile.

## 2. Ketotifen:

- It is absorbed orally.
- Bioavailability is 50% due to first pass metabolism.
- It is largely metabolized.
- Plasma half life is 20-22 hours.

## MAST CELL STABILIZERS: MECHANISM OF ACTION

- These drugs inhibit degranulation of mast cells.
- Release of mediators like Histamine, LT, PAF, IL is inhibited.
- This action may include delayed Cl channel.
- Chemotaxis of inflammatory cells is inhibited.
- Bronchial hyperactivity is reduced.
- Bronchospasm due to various stimuli (allergens, irritants, cold air and exercise) is prevented.
- It can't be used to prevent attack of asthma because it does not affect the constrictor action of histamine.

## MAST CELL STABILIZERS: USES

- Sodium cromoglycate:
  1. Bronchial asthma: It is used as a long term prophylactic in mild to moderate asthma. Decrease in frequency and severity of attacks and improvement in lung function is more likely in extrinsic asthma. Improvement in lung function occurs within 2-4 weeks slowly and lasts 1-2 weeks after discontinuing.
  2. Allergic rhinitis: Sodium cromoglycate is not a nasal decongestant. But 4 times daily use as a nasal spray can produce symptomatic improvement in 4-6 weeks.
  3. Allergic conjunctivitis: Regular use as eye drops is beneficial in some chronic uses.

## MAST CELL STABILIZERS: USES

- Ketotifen:
  1. After 6-12 weeks of use, it reduces symptoms in about 50% patients of bronchial asthma.
  2. But lung function improvement is marginal.
  3. It also produces symptomatic relief in patients with Atopic dermatitis, Perennial rhinitis, Conjunctivitis, Urticaria and Food allergy. Thus, it is essentially indicated in patients with multiple disorders.



## MAST CELL STABILIZERS: ADVERSE EFFECTS

- Sodium cromoglycate: It is poorly water soluble, so poorly absorbed and systemic toxicity is minimal. Rare side effects are:
  1. Bronchospasm
  2. Throat irritation
  3. Cough
  4. Headache
  5. Dizziness
  6. Arthralgia
  7. Rashes
  8. Dysuria

## MAST CELL STABILIZERS: ADVERSE EFFECTS

- Ketotifen: Generally this drug is well tolerated. Rare side effects are:
  1. Sedation
  2. Dry mouth
  3. Dizziness
  4. Nausea
  5. Weight gain

## MAST CELL STABILIZERS: DOSAGE

- Sodium cromoglycate:
  1. FINTAL inhaler: 1 mg metered dose aerosol, 2 puff 4 times daily.
  2. FINTAL nasal spray
  3. FINTAL eye drops.
- Ketotifen:
  1. ASTHAFEN: 1 mg tablet, 1mg/ 5ml syrup.

# CORTICOSTEROIDS

- MECHANISM OF ACTION
- SYSTEMIC STEROID THERAPY
- INHALED STEROIDS
- PRECAUTION OF USING CORTICOSTEROIDS
- INDIVIDUAL DISCUSSION ON INHALED STEROIDS

# CORTICOSTEROIDS: MECHANISM OF ACTION

- Glucocorticoids are not bronchodilators.
- They act by reducing-
  1. Bronchial hypersensitivity.
  2. Mucosal edema.
  3. Inflammatory response to AG-AB reaction.
- Corticosteroids produce more complete and sustained symptomatic relief than bronchodilators and cromoglycates.

# CORTICOSTEROIDS: SYSTEMIC STEROID THERAPY

- Systemic steroid therapy is applied in two following cases:

1. Severe chronic asthma: When it is not controlled by bronchodilator and inhaled steroids or when recurrences or severities occur.

\_\_\_\_\_ \*In these cases start with prednisolone 20-60 mg daily.

\_\_\_\_\_ \*Then reduce the dose after 1-2 weeks of good control.

\_\_\_\_\_ \*Finally try shifting the patient onto an inhaled steroid.

2. Status asthmaticus: When it is not controlled by intensive bronchodilator therapy.

\_\_\_\_\_ \* Start with a high dose of rapidly acting glucocorticoid therapy.

\_\_\_\_\_ \* Then reduce the dose after 5-7 days of good control.

\_\_\_\_\_ \* Then discontinue suddenly.

## CORTICOSTEROIDS: INHALED STEROIDS

- The drugs are:
  1. Beclomethasone dipropionate
  2. Budesonide
  3. Fluticasone
  4. Ciclesonide
- It has been suggested that inhaled steroids should be the STEP 1 drug for all asthma patients because *airway inflammation and bronchial development starts from the beginning.*
- *But* practically they are introduced only when the disease is not only episodic and inhaled  $\beta_2$  agonists are required daily.

# PRECAUTION OF USING CORCICOSTEROIDS

- Inhaled steroids have no role during acute attacks of asthma.
- **Their main role is to prevent acute attacks of asthma** by suppressing bronchial inflammation, increase peak expiratory flow rate and reduce need for rescue of inhaled  $\beta_2$  agonists.
- Peak effect is seen after 4-7 days of starting inhalation and benefit exists for a few weeks after discontinuation.
- **The main danger of using corticosteroids is that: When patients have to be switched over from oral steroids, they should receive inhaled steroids for additional 1-2 weeks before the oral steroid therapy is discontinued. Otherwise, sudden steroid discontinuation may manifest:**
  1. ***Precipitation of asthma***
  2. ***Muscular pain***
  3. ***Depression***
  4. ***Hypotension***
  5. ***Tiredness***



# INDIVIDUAL DISCUSSION ON INHALED STEROIDS

STEROIDS	FEATURES	USES	DOSAGE
BUDESONIDE	A nonhalogenated glucocorticoid with high topical: systemic ratio, rapidly metabolized.	<ul style="list-style-type: none"><li>• Asthma</li><li>• Allergic rhinitis</li></ul>	<ul style="list-style-type: none"><li>• 200-400 microgram BD by inhalation.</li><li>• 200-400 microgram/day by spray.</li></ul>
FLUTICASONE	This newer drug has high potency and longer duration.	Asthma	100-250 microgram BD/day
FLUNISOLIDE		Seasonal and perennial rhinitis.	25 microgram per nasal spray
CICLESONIDE	It is a prodrug that is cleaved by esterase.	Asthma	80-160 microgram by inhalation OD.

# ANTI-IGE -ANTIBODY

- DRUG
- USE
- MECHANISM OF ACTION

# ANTI-IGE –ANTIBODY: DRUG

- OMALIZUMAB

## ANTI-IGE –ANTIBODY: USE

- It is used only in severe extrinsic asthma.
- It is very expensive, so use of it is restricted for:
  1. Resistant asthma patients.
  2. Patients giving positive skin test.
  3. Patients with raised IgE level who require frequent hospitalization.

## ANTI-IGE –ANTIBODY: MECHANISM OF ACTION

- The drug omalizumab is actually a humanized monoclonal antibody.
- It is administered i.m or s.c.
- It neutralizes free IgE in circulation without activating mast cells and other inflammatory cells.
- So IgE level in plasma is down and so, mast cell-IgE mediated histamine (inflammatory mediators) release is inhibited.
- So bronchoconstriction occurs.

# CHOICE OF TREATMENT

1. Mild episodic asthma: Symptoms less than once daily: Inhaled short acting  $\beta$ 2 agonists at onset of each episode.
2. Seasonal asthma: Regular cromoglycate/ low dose inhaled steroid (200-400 microgram/ day)
3. Mild chronic asthma with occasional exacerbation: Symptoms once daily: Inhaled low dose inhaled steroid + cromoglycate.
4. Moderate asthma with frequent exacerbation: Occurs >1 daily: Increased dose of inhaled steroid ( upto 800 microgram/ day) + Inhaled long-acting  $\beta$ 2 agonist.
5. Severe asthma: Continuous symptoms: Regular high dose of inhaled steroid (2000 microgram/ day) + inhaled long-acting  $\beta$ 2 agonist twice daily.
6. Status asthmaticus:

1. Hydrocortisone hemisuccinate (or any equivalent dose of glucocorticoid) 100 mg i.v followed by 100-200 mg 4-8 hourly infusion.
2. Nebulized salbutamol (2.5-5 mg) + Ipratropium bromide (.5mg) intermittent inhalation driven by O<sub>2</sub>.
3. High flow humidified oxygen inhalation.

Then if needed,

1. Salbutamol/ Terbutaline .4 mg i.m/ s.c.
2. Inhalation and mechanical ventilation.
3. Treat chest infection with extensive antibiotic therapy.
4. Correct dehydration and acidosis with ( Normal saline + Sodium bicarbonate) infusion.

Thank you....