Disorders of respiratory system

Main disorders of Respiratory system:

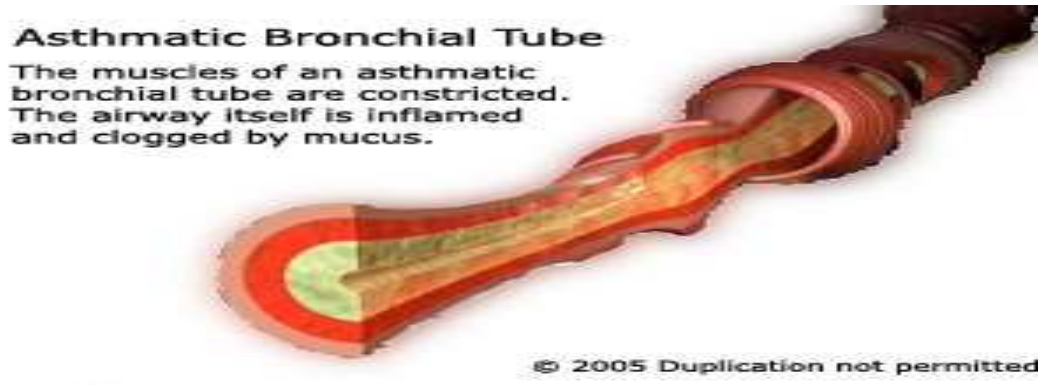
1. Bronchial asthma.
2. Cough.
3. Adult respiratory distress syndrome.

ΑΣΤΗΜΑ:

-Recurrent attacks of airway obstruction in response to external stimuli.

-Autoimmune disease.

-Chronic inflammatory disorder of airways.



➲Three changes occur inside the airways of the lung in people with asthma:

1) Inflammation or swelling, whereby the airways become inflamed & produce a thick mucus.
2) Bronchospasm constriction of the muscles around the airways, causing the airways to become narrow.
3) Airway hyperactivity: abnormal sensitivity of the airways to wide range of external stimuli as pollen, cold air & tobacco smoke.

➲Symptoms:

1) Immediate response (bronchospasm).
2) Late response :
    - Bronchospasm
    - VD
    - Inflammation
    - mucus secretion
3) cough.
4) dysnea.
5) wheezing.

➲Causes:

A -Extrinsic asthma (Allergic Asthma).
B-Intrinsic asthma:
- Infection
- Stress
-cold air (Exercise Asthma)
- Drugs as aspirin (Iatrogenic Asthma).

➲Airways Innervation:

1) <u>EFFERENT:</u>

- No sympathetic supply.
    - β2 in :
        - smooth muscles (relaxation)
        - glands (↓ secretion)
        - mast cells(stabilization)
        - increase mucociliary clearance.
- Parasympathetic supply:
    - M3 receptors in smooth muscles & glands.

(so, we have to stop the action of parasympathetic system)

2) <u>AFFERENT:</u>

- Irritant receptors (vagal fibers) → upper airways.
- C-fiber receptors (sensory fibers) →lower airways.

Rationale for pharmacological intervention:

- Reduction of mast cell degranulation:
  - sympathomimetic agents.
  - Ca++ channel blockers.
  - cromolyn / nedocromil.

- Decrease cholinergic influence from vagal motor nerves:
  - Antimuscarinic agents.

- Direct relaxation of airway smooth muscle:
  - sympathomimetic agents.
  - Xanthine derivatives.

I-Bronchodilators:

(They reverse the bronchospasm of immediate phase)

- B2 agonists.
- Xanthine preparations.
- cantimuscarinic.

II-Anti-inflammatory:

✓ (prevent the inflammatory components of both phases)

- mast cell stabilizers.
- glucocorticoids.
- leukotriene antagonists (LT-antagonists):
  - 5-lipoxygenase inhibitors.
  - leukotriene receptor antagonists.

ॐ SYMPATHOMIMETICS:

Mechanism of action:

1-relax airway smooth muscles (direct β2 stimulation).
2-inhibits mediators release from mast cells.
3-increase mucus clearance by:
- increasing ciliary activity
- affecting composition of mucus secretion → ↓ viscosity.

4-increase cAMP → bronchodilation (stimulate adenyl cyclase enzyme)

Classification:

A- Non selective B agonists:

- Epinephrine
- isoprenaline
- Orciprenaline
- Ephedrine

B- Selective B2 agonists:

- Salbutamol
- Terbutaline
- Salmeterol
- Albuterol
- Metaproterenol

✹Epinephrine

- Potent .
- Rapid action (15min).
- S.C or by aerosol inhalation .
- Useful in asthma emergency but now typically superseded by β2 selective agonist

☠Disadvantages :

1. non effective orally .
2. hyperglycemia ≠ in diabetics.
3. CVS side effects : Tachycardia, arrhythmia .
4. Exacerbate angina.

✹Isoprenaline

- Potent bronchodilator
- Inhalation by aerosol.
- Rapid action (within 5 min)

☠Disadvantages :

1. Short duration (60-90 min)
2. CVS side effect (arrhythmia)
3. Ineffective orally (1^{st} pass).

✹Orcirendine

(non-catecholamine)

- Effective orally (20 mg every 6 hr)
- Delayed onset of action.
- Long duration of action .
- Effective by inhalation with rapid onset .

☠Disadvantages:

- As epinephrine.

✹Ephedrine

(dual action)

- Effective orally 25 mg /6 hr
- Delayed onset of action.
- Longer duration of action

☠Disadvantages :

1) Insomnia, nervousness, tremor.
2) CVS side effect . used only prophylactic between attacks.
3) Tachyphylaxis (depletion of mediator + down regulation)
   (or tolerance بصورة عامة)
4) Less potent.

Selective β_2 agonists

- first choice in acute attack **
- has longer duration of action than non-selective**
- the same potency as isoprenaline**

1. Most effective drugs (by inhalation) for treatment of acute bronchospasm & for prevention of exercise – induced asthma
2. Effective :
   - orally or
   - by inhalation
3. Inhalation of aerosol, powder or nebulized solution
4. Oral route leads to →systemic side effects
5. Routes of administration:
   - Inhalation
   - Oral: albuterol, metaproterenol, terbutaline
     Side effects: sk. Muscles tremor, nervousness
   - Injection:
     - IV (salbutamol)
     - SC (terbutaline → used for asthma emergency in the absence of aerosol availability)
6. Rapid onset of action (30 min if orally, 5 min if inhalation)
7. Long duration of action (3-4 h) up to (12 h with salmeterol)
8. Minimal CVS side effects
9. Suitable for hypertensive patients**
10. Effective in asthma with heart failure**

Disadvantages:

- Sk. Muscles tremor
- Tolerance (β-receptor down-regulation)
- Tachycardia (β_1 stimulation)

☒ Short-acting β_2 agonists:

- Salbutamol (IV)
- terbutaline (SC)
- Albuterol
- metaproterenol

- Used for acute attacks of asthma
- Salbutamol used during severe attacks → status asthmaticus (IV)
- Premature labor (IV) as adverse effect

☒ Long-acting β_2 agonists

(**Salmeterol**)

- Long duration of action (12 h or more)
- Potent β_2 agonist
- Why long duration? Due to high lipid solubility (creates a depot effect)
- Routes: oral, inhalation → greatest airway effect, parentral

➲**Used for prophylaxis of nocturnal asthma******

Anti-muscarinic agents

1) Ipratropium

2) oxitropium → Quaternary derivatives of atropine :

- not lipid soluble
- not absorbed orally
- no CNS side effects as with atropine which is tertiary compound)

✓ Blocks all subtypes of muscarinic receptors

Pharmacokinetics:

- Not absorbed orally
- Given by aerosol inhalation
- Delayed onset of action (30 min)
- Duration (3-5 h)

Pharmacodynamics:

- Bronchodilatation
- No effect on late inflammatory phase
- Less effective than β_2-agonist
- Minimal systemic side effects

Uses:

- Adjunct to β_2-agonist & steroids for acute asthma
  (It's not effective alone , so we give in combination)
- COPD
- **β-blockers induced bronchospasm (drug of choice)**

Methylaxanthines

- Theophylline (most potent)
- Theobromine
- Caffeine

➲Aminophylline =theophylline + ethylene diamine → given I.V.

Mechanism of Action:

1) are phosphodiestrase inhibitors:
   ↑ cAMP → bronchodilation , platelet aggregation, (+) heart
2) Adenosine receptors antagonists (A1):
   "relaxation of smooth muscle, ↓ histamine release (mast cell stabilization)"
3) Anti inflammatory action →(Stabilization of mast cell membrane).
4) Increase diaphragmatic contraction (direct effect).

Pharmacological Effects :

1- Anti asthmatic action .

2- CNS stimulation:

- Decrease of fatigue & elevation of mood. ***
- Tremors, nervousness, Insomnia.
- Respiratory Stimulant.
- Toxic dose → convulsion.

3-Relaxation of smooth muscles bronchial, intestinal, uterine and blood vessels.

4- GIT : Increase gastric acid and digestive enzymes secretions.

5-CVS:

Direct Effect :

Heart : + ve Inotropic + ve chronotropic.

BP: Direct vasodilatation except cerebral b.v.

BP: Normal dose → insignificant increase.

Large dose → Severe hypotension and arrhythmia.

6- Kidney :

- weak diuretic action.

- ↑ GFR → due to afferent glomerular dilatation.

7- SK. muscle : ↑ diaphragmatic contraction → improve ventilation.

✹Pharmacokinetics

1- Well absorbed orally (must be given after meals).
2- Metabolized in the liver (t ½ = 8 h).
3- Low therapeutic index.

➲ **T ½ is decreased by :**

1) Smoking & drinking.
2) Children.
3) Enzyme inducers (rifampicin, phenobarbitone - phenylbutazone).

➲ **T½ is increased by**

1. Liver dysfunction.
2. Hepatic blood flow (CHF, B-blockers).
3. Renal disease (10 % is eliminated). Enzyme inhibitor (Cimetidine, erythromycin, ketoconazole, O.C. pills).

➲Clinical Uses:

1. Second line drug in asthma (orally as sustained - release preparation).
2. For status asthmaticus (slow infusion) aminophylline (theophylline + ethylene diamine).

Side Effects:

1- CNS side effects: Insomnia, nervousness.
2- GIT disturbance: nausea, vomiting, anorexia.
3- Low therapeutic index or narrow safety margin
Monitoring of theophylline level is necessary (5 -20 mg / L).
4- CVS effects: Hypotension, arrhythmia, Cardiac arrest.

ॐAnti - inflammatory Agents

✓ These inhibitors prevent the inflammatory components of both phases.

1) Mast cell stabilizers.
2) Glucocorticoids.
3) Leukotrienes antagonists.
    a) 5-Lipoxygenase inhibitors.
    b) Leukotriene–receptor antagonists.

Anti-inflammatory agents:

- Are not bronchodilator
- Have No direct effect on bronchial smooth muscles
- Not effective in terminating acute attack of asthma.
- Used as prophylactic medications (inhalation)
- Effect usually attained after 2-4 weeks (Late).
- Maximum action at 9-12 months.

❶Glucocorticoids

✖Mechanism of Actions:

- reduction of phospholipase A2
- reduction of antigen antibody reaction
- mast cell stabilizer
- decrease capillary permeability and mucosal edema
- up regulation of B2 receptors (additive effect to B2 agonists)

❍Pharmacokinetics :

- Orally taken : methylprednisolone, prednisone
- inhalation: fluticasone, beclomesthasone ,budesonide, triamcinolone
- Injection: hydrocorticosone, dexamethasone

❍Pharmacodynamics :

- not bronchodilators (so not effective in acute phase)
- used as prophylactic medications (inhalation) to decrease the frequency of attacks
- effect usually attained after 2-4 weeks (late)
- maximum action at 9-12 months
- decrease the inflammatory components of immediate and late phase
- decrease bronchial hyperactivity
- effective in exercise and allergic induced asthma

◎Inhalation:

- regular use :
  - suppress inflammation
  - decrease bronchial hyper response
  - decrease asthma symptoms in patients with chronic disease
- decrease need for oral corticosteroids in patients with severe asthma
- maybe used as 1st line for mild asthma combined with B agonists

(10-12) weeks then re evaluate dosage s maybe with time decreases

some patients may be able to stop using the drug completely

Clinical uses:

- due to significant adverse effects associated with chronic corticosteroids administration oral /parental corticosteroids are used:
  1) management of acutely ill patients
  2) patients not adequately maintained with bronchodilators
  3) patients whose symptoms are worsening despite reasonable maintenance

Clinical Uses:

1- first line therapy in moderate to sever asthma (inhalation)
2- status asthmticus (IV)
3- prophylaxis

Side effects:

1- orally: “oral corticosteroids produce systemic effects”
   - adrenal suppression
   - growth retardation
   - decrease bone density
   - cataract formation
   - dermal thinning
   - glaucoma
2- inhalation: “has less side effects”
   - oral candidiasis (thrush)
   - dysphonia (voice hoarseness)

❷ Mast Cell Stabilizers

i. Soduim cromoglycate

ii. nedocromil

✓ Acts partially by stabilization of mast cell membrane

Pharmacokinetics :

1- inhalation (aerosol ,powder, nebulized solution)

2- 10% absorbed

3- T1/2=90 min

4- excreted unchanged 50% urine 50%bile

Pharmacodynamics :

1- no bronchodilation

2- decrease inflammatory of immediate and late phase

3- decrease bronchial hyper reactivity

4- effective in exercise antigen and irritant induced asthma**

5- children respond better than adults**

Clinical Uses:

1) prophylaxis in asthma especially in children
2) allergic rhinitis
3) conjunctivitis
4) contraindicated in acute attack (reflex airway obstruction)***

Side Effects:

a) minor URT irritation cough burning sensation nasal congestion
b) hypersensivity reactions

❸ Leukotrienes antagonists

a) 5-lipo oxygenase inhibitors → inhibit synthesis.

b) leukotriene receptor antagonist → inhibit action.

Leukotriene production:

- Action to 5-lipo oxygenaseon arachidonic acid.
- Synthesized by inflammatory cells found in the airway,including:
  - Esinophils
  - Macrophages
  - mast cells
  - basophils.

- Leukotriene B4→neutrophil chemoattractant.

- Leukotriene C4 & D4:
  - Bronchoconstriction.
  - Mucosal edema.
  - Mucus hypersecretion.
  - ↑ bronchial reactivity.

✹ 5-lipo oxygenase inhibitors

Zeiluton

✓ Block the production of:

- Spasmogenic leukotrienes (LTC4 & LTD4).
- Chemotaxin (LTB4).

➲ " both anti-inflammatory & bronchodilator"

✓ Given orally→ only orally.**

➲ " theophylline & LT antagonists are NOT given by inhalation"

- Short duration of action.
- Short T1/2 (3-4 times/day).
- Reduces late phase of inflammation.
- Mild to moderate asthma.
- Potentiate corticosteroid actions (low dose of corticosteroid can be given).

✹ Leukotriene-receptor antagonists

1) Zafirlukast
2) Montelukast.
3) Pranlukast
4) Cinalukast.

- Potent competitive antagonists of LT D4-receptors.

➲ No anti-inflammatory action BUT it's bronchodilator.

- Taken orally. (only)
- Less effective than inhaled beclomethasone.
- Bioavailability reduces significantly with food (Zafirlukast).

Clinical Uses:

Bronchodilators (1/3 of salbutamol).

1) mild asthma.
2) aspirin induced asthma.
3) prevention of antigen & exercise induced bronchospasm.

Dose:

✓ 20 mg twice daily.

👽 Adverse effects of LTs antagonist:

→ both zeiluton , zafirlukast.

- Less effective than corticosteroids.
- Elevation of liver enzymes . → more in zeiluton than zafirlukast.**
- Headache.
- Dyspepsia.
- Churg-strauss syndrome → rarely. Manifested as vasculitis, asthma ,etc.
- Cough**

a) Physiological cough (productive cough):

- Is a protective reflex mechanism that removes foreign material & secretions from the bronchi & bronchioles.

b) Unproductive cough:

- Occurs due to → exposure to irritant vapors or gases or due to pathological conditions as chronic bronchitis.

ॐAnti-tussives

→ in dry cough.

①Peripheral antitussives: eg: benzonatate.

- block the cough peripherally through blocking the stretching receptors in the lung.

②central antitussives:

a) Narcotic analgesics:
   - morphine
   - codeine
   - methadone
   - hydrocodone.

b) synthetic narcotic analgesics

c) anti-histaminics (H1 blockers).

◎Narcotic analgesics

✓ are drugs used to suppress dry cough.

- Codeine:

1) opiate with less addiction liability.
2) potent antitussive.
3) weak analgesic.

👽Adverse effects:

- constipation.
- inhibition of mucociliary clearance (thick sputum).
- decrease secretion in the bronchioles.
- drowsiness & mild respiratory depression.
- *dependence*.
- dry mouth.

◎Synthetic narcotic analgesics

- Dextromethorphan
- levopropoxyphene.

✹ Dextromethorphan:

➲ as compared to codeine is :

1) as potent as codeine.
2) no drowsiness.
3) less constipating effect.
4) no respiratory depression.
5) no inhibition of mucociliary clearance.
6) no addiction.

◎Anti-histaminics (H1 blockers)

- Diphenhydramine
- Triprolidine

Adverse effects:

1) Anticholinergic actions.
2) Sedation.
3) Drowsiness.

Contraindicated in:

1) Chronic bronchitis.
2) Cough associated with asthma
3) (harmful sputum thickening & retention).

Notes:

- Antitussives are used for dry cough.

ॐExpectorants

- Are drugs used to facilitate expulsion of secretions & exudates from the respiratory passages by cough.

Classification

1) **Sedative Expectorants**

- They increase the fluidity of sputum & its expulsion by cough.
  - Potassium citrate
  - Potassium acetate
  - Ammonium chloride
  - Ipecaquanha
  - Na & K iodide
  - Guaiacol

✓ They can be used for inflammatory condition of respiratory mucosa due to their smoothing effect).

2- Stimulant expectorants

These drugs are used in chronic inflammation of respiratory mucosa (chronic bronchitis).

e.g. trepene → hydrate → guaiacol.

✓ They promote healing and repair of mucosal tissues

ॐMucolytics

- they break down the mucus.

➲ Acts by decreasing viscosity of sputum.

acetyl cysteine

✓ (interfering with disulphaide bonds in mucus).

→ giving regular compounds.

bromohexine

✓ (destroy mucopolysaccharid structure of mucus).

→giving irregular compounds.

stem inhalation.

Clinical Uses:

1) acute & chronic bronchitis.
2) asthma.

The End :)

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