Chapter 8

Respiratory Pharmacology

Ebrahim said behairy

Chapter 8 Respiratory Pharmacology

Part 1: Agents used to treat cough

Types of cough:

1. **Dry cough (non-productive or useless cough):**
   - It should be treated by cough suppressants (ANTITUSSIVES).
2. **Productive cough (wet or useful cough):**
   - It should be encouraged by agents that render secretions more easily removable e.g. (MUCOLYTICS and EXPECTORANTS).
   - It is suppressed only if it is dangerous to the patient e.g. after eye surgery.

Antitussives

Definition: they are drugs that reduce the frequency or intensity of coughing.

Classification:

ANTITUSSIVES

A. PERIPHERAL	B. CENTRAL		C. PERIPHERAL AND CENTRAL
	1. Narcotic antitussives:	2. Non-narcotic antitussives:	Benzonatate Carbetapentane
1. Demulcents: (e.g. liquorice lozenges)	Codeine Pholcodeine	Dextromethorphane Noscapine Levopropoxyphen	
2. Steam inhalation: of tincture benzoin Co. or menthol			

A. PERIPHERAL ANTITUSSIVES: they ↓ afferent impulses of the cough reflex.

- **Demulcents (e.g. liquorice lozenges):**
  - They form gelatinous protective coat on the inflamed mucous membranes.
  - They are used when the cough arises from **above** the larynx i.e. pharyngitis.
- **Steam inhalation of menthol or tincture benzoin Co.:**

- They are added to boiling water and the warm steam is inhaled to stimulate secretion of mucus that forms a protective coat on the inflamed mucous membranes.
- They can be used when the cough arises from **above or below** the larynx.

B. CENTRAL ANTITUSSIVES: they inhibit cough center in the medulla.

I. Narcotic antitussives:

1. CoDeine:

- It is a *natural* Derivative of morphine (*methyl morphine*).
- It causes Direct inhibition of the cough center in the medulla.
- It has weak (Delicate) analgesic action.

Adverse effects:

- Drowsiness, nausea, vomiting and Constipation.
- Dryness of mucosa and thickening of sputum (Difficult to expel).
- Drug Dependence (aDDiction) if used for long Duration.
- Depression of respiratory center if used in overDoses.

2. Pholcodeine:

- It is *semisynthetic* derivative of morphine.
- It is less addictive than codeine.

N.B.

Some antihistamines (diphenhydramine) have antitussive activity, the mechanism is unknown. It has undesirable **atropine-like effect** → drying of mucosal secretions.

II. Non-narcotic (non-addictive) antitussives:

1. *Dextro*-methorphan:

- It is *synthetic* derivative of morphine.
- It has selective central antitussive action **without** significant opioid effects (i.e. No addiction liability, No analgesic action, No resp. depression, No constipation).

2. *Levo*-propoxyphen:

- It has selective central antitussive action **without** significant opioid effects.

3. Noscapine:

- It is *natural* derivative of morphine.
- It has selective central antitussive action **without** significant opioid effects.
- It has papaverine-like action leading to **relaxation** of bronchial smooth ms.

CENTRAL AND PERIPHERAL ANTITUSSIVES:

Benzonatate and carbetapentane:
Both drugs depress peripheral cough receptors at the lung by their local anesthetic effect, so they inhibit transmission of afferent impulses to cough center, they also have central antitussive effect.

Mucolytics

Definition: mucolytics are agents that reduce viscosity (liquefaction) of respiratory tract secretions without increasing their amount.

- **Bromhexine (Bisolvon®):**
  It reduces the viscosity of bronchial secretion by fragmenting its glycoproteins (depolymarization) so mucus becomes less viscid and easily to expel.

  Uses:
  - Chronic respiratory diseases (chronic bronchitis, emphysema, bronchiectasis and cystic fibrosis).
  - Acute respiratory disease (acute bronchitis, pneumonia and asthma).
  - Post-operative and post-traumatic pulmonary complications.
  - Chronic sinusitis.
  - Chronic otitis media.

- **Ambroxol (Mucopect®):** it is metabolite of bromhexine and less gastric irritant.

- **Acetylcysteine:**
  It has free sulfhydryl (-SH) groups, that break disulfide bonds in mucous and reduce its viscosity. It could be given orally or by inhalation.
  Uses: the same uses as bromhexine.

- **Iodides:** they potentiate the effect of proteolytic enzymes in the sputum.

- **Enzymes:** e.g. trypsin, chymotrypsin, streptokinase.

- **Water vapor:** inhalation of water vapor is excellent expectorant and mucolytic.

- **Cough mixtures:**
  Many preparations used for common cold, contain more than one ingredient e.g. expectorant, bronchodilators, nasal decongestants and antihistamines to control different symptoms of common cold.

▶ **Cough mixtures should have the following criteria:**

- They must be used only when multiple symptoms are present.
- No more than three active ingredients from different pharmacological groups should be mixed.
- Each active ingredient must be present in sufficient concentration.

Expectorants

Definition: drugs that increase the amount and liquefy bronchial secretions. This action facilitates the removal of respiratory tract secretions and other irritants.

- **Alkaline expectorants: (e.g. Na^+ or K^+ citrate and acetate):**
  They increase the alkali reserve of the blood. The excess Na^+ or K^+ is excreted through the bronchial glands with excess watery mucous which become less sticky and easy to expel. They are used in the early dry stage of acute bronchitis.

- **Nauseant expectorants: (e.g. tincture ipecacuanha and NH_4Cl):**
  They stimulate sensory nerve endings in the stomach leading to reflex stimulation of excess bronchial secretion. They are used in the early dry stage of acute bronchitis.

- **Iodides: (sodium and potassium iodide):**

- Expectorant effect: iodides accumulates in the bronchial glands and stimulate secretion of low viscosity watery mucous.
- Mucolytic effect: iodides also potentiate the effect of *proteolytic enzymes* in the sputum and liquefying it.

- Adverse effects:
  - **Metallic taste.**
  - Irritation of lachrymal, nasal and salivary glands and increase their secretion.
  - Irritation of gastric mucosa and painful salivary swelling.
  - Thyroid dysfunction (hypothyroidism).
  - Allergic reactions and ulceration of mucous memb.

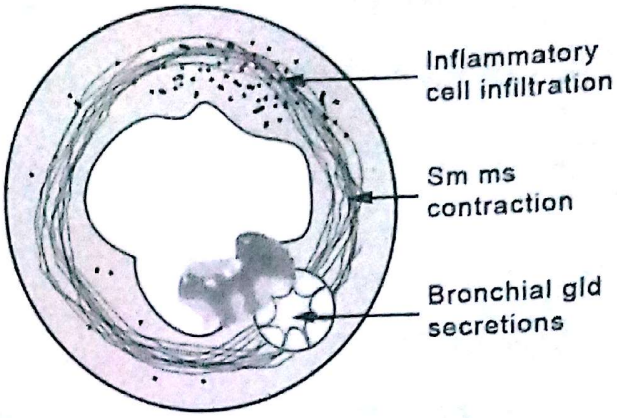
- **Guaifenesin:** It increases bronchial secretions and facilitates its expectoration.

Part 2: Treatment of bronchial asthma

Definition: functional airway obstruction due to **hyperreactivity of the airway** muscles to variety of stimuli.

Pathogenesis:

Frequent exposure to allergic stimuli causes infiltration of the bronchial wall by acute and chronic **inflammatory cells**. These cells release many **inflammatory mediators** e.g. histamine, adenosine, PGs, LTs, PAF, etc. leading to:



- Contraction of airway sm ms
- Increased mucus secretion that is difficult to expel.
- Congestion and edema of the respiratory mucosa.

Predisposing factors:

- **Genetic factors:** asthma occurs in families with positive history of allergy.
- **Respiratory infection:** bacterial or viral.
- **Psychological factors:** are present in 40 % of asthmatics.
- **Exercise:** bronchospasm is induced by ventilation of **cold air**.
- **Drugs:** can cause bronchospasm by 2 methods:
  - As an allergic response: e.g aspirin *(aspirin- induced asthma)*.
  - Direct bronchoconstriction: e.g cholinomimetics, non-selective β-blockers, $PGF_{2\alpha}$, and histamine releasers (curare, trimetaphan, morphine, etc).

Classification of bronchial asthma:

A. According to aetiology:

- **Extrinsic asthma (allergic):** It is due to allergy to antigenic substances in the inspired air e.g. pollens, animal feather, drugs, or home dust mite.
- **Intrinsic asthma (non-allergic):** bronchospasm can be evoked by internal causes. It is common above 40 years and have bad prognosis.

B. According to clinical severity:

- **Mild asthma:** patient has bronchoconstrictive episodes <2 times/week and is asymptomatic between attacks.

- **Moderate asthma:** patient has bronchoconstrictive episodes >2 times/week and symptoms requiring inhaled beta agonists daily.
- **Severe asthma:** patient has continuous symptoms, Hospitalization may be required.

C. According to clinical presentation:

- **Acute asthma.**
- **Chronic asthma.**
- **Acute severe asthma (status asthmaticus):** is a condition in which bronchodilators are ineffective in relieving the attack after 24 hrs.

Investigations:

- **Chest X-ray.**
- **Lung functions:** e.g. forced expiratory volume (FEV) (it is 80% of predicted in mild asthma, 60-80% in moderate asthma & <60% in severe asthma).
- **Blood samples:** for blood gases, pH and electrolytes.
- **ECG:** to differentiate between cardiac asthma and bronchial asthma.

Lines (objectives) of treatment:

- **Bronchodilatation.**
- **Reduction of bronchial inflammation and hyperreactivity.**
- **Prophylactic treatment to prevent recurrence.**
- **Prevention of exposure to precipitating factors.**
- **Other measures.**

Bronchodilatation

3 GROUPS of bronchodilator drugs:

- **β-adrenergic agonists.**
- **Muscarinic receptor blockers:** e.g. **ipratropium.**
- **Xanthines** e.g. **aminophylline.**

1. β-adrenergic agonists

- **Non-selective β-receptor agonists:** e.g. adrenaline, isoprenaline and ephedrine.
- **Selective β_2 agonists:**

  Short acting: salbutamol, terbutaline, fenoterol (duration 3-4 hrs).

  Long acting: salmeterol and formoterol (duration 12 hrs).

Mechanism of action:

- Stimulation of bronchial β_2 receptors → ↑ cAMP → bronchodilatation.
- Stimulation of β_2 receptors in the mast cells → ↓ histamine release
- They ↓ capillary permeability and bronchial wall edema.

Dose and administration:

- In acute asthma: selective β_2 stimulants are given by **inhalation or i.v infusion.**
- In chronic asthma: selective β_2 stimulants are given **orally** 2-4 mg/8-12 hrs.

Side effects:

- Tachycardia and arrhythmia due to:
  - *Reflex from hypotension (caused by VD of sk ms BV).*
  - *Direct activation of cardiac β_1 (due to loss of selectivity in high doses).*
- Tremors of skeletal ms and nervousness.
- Tolerance with prolonged use *(requiring temporary cessation of the drug).*
- Hypokalemia *(due to shift of K^+ from blood to cells).*

2. Muscarinic antagonists: Ipratropium bromide

Atropine blocks M_3 receptors in airway ms leading to bronchodilatation through unopposed β_2 action but **it is not preferred for treatment of asthma. Why?**

- It is non-selective M_3 blocker leading to many side effects e.g. dry mouth and urine retention.
- It can cross BBB and causes CNS side effects.
- It causes excessive dryness of bronchial secretions that become difficult to expel.

▶ **Ipratropium is more preferred than atropine because:**

- It is more selective bronchodilator than atropine.
- It is quaternary ammonium compound that can't cross BBB and has no CNS side effects.
- Does not cause excessive dryness of the bronchial secretions.

▶ **Ipratropium is not sufficient alone for bronchodilatation.** It is usually combined with **β_2 agonists** because:

- To make synergism with the β_2 agonist.
- To obtain longer duration of action.

3. Xanthines

Classification:

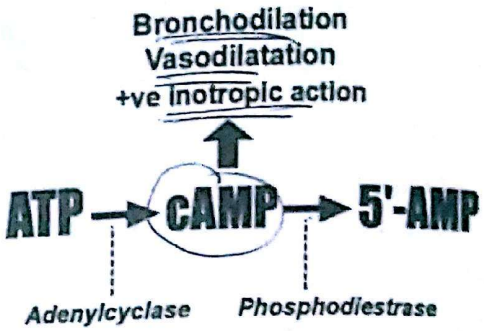
- **Natural:** e.g. caffeine, theophylline, and theobromine.
- **Synthetic:** e.g. aminophylline (theophylline + ethylene diamine).

Pharmacokinetics:

- Oral absorption is good while rectal absorption is irregular.
- Elimination occurs by hepatic metabolism.
- Metabolism is reduced by enzyme inhibitors (e.g. erythromycin and cimetidine) and increased by enzyme inducers (e.g. smoking, rifampin, and phenytoin).

Mechanism (as bronchodilators):

1. They inhibit **phosphodiestrase** (PDE) enzyme → ↑ cAMP → bronchodilatation.
2. They block **adenosine receptors** (P_1 or A_1 purinoceptors) → prevent the potent bronchoconstrictor effect of adenosine.
3. They ↑ catecholamines release from adrenal medulla and ↓ COMT enzyme.
4. They have mild anti-inflammatory and immunomodulating effects leading to ↓ cell infiltration and cytokine release.



Drugs that inhibit PDE enzyme:

1. **Sildenafil** (↓ PDE t5 in the corpus cavernosum) → ttt of erectile dysfunction.
2. **Inamrinone and milrinone** (↓ PDE t3 in the cardiac ms) → +ve inotropic action.
3. **Methylxanthines** (↓ PDE in the bronchial sm ms) → bronchodilatation.
4. **Papaverine** (↓ PDE in the intestinal and genitourinary sm ms) → relaxation

Pharmacological effects:

Respiratory: bronchodilatation and mild anti-inflammatory action.

CNS effects:

- Diffuse CNS **stimulation:** cortex, medullary centers: vasomotor, vagal, and respiratory.
- VC of cerebral vessels (useful in the treatment of migraine).
- Delay fatigue and increased power of concentration and alertness.
- Large doses produce headache, insomnia, and convulsions.

CVS effects:

- +ve inotropic and chronotropic action.
- Arrhythmias and extrasystoles (all PDE inhibitors are arrhythmogenic).
- VD of all arteries (e.g. coronary and peripheral vessels) except cerebral (VC).

Smooth muscles: relaxation of renal, GIT, and bronchial sm ms.

GIT: ↑ HCl and pepsin secretion.

Kidney: ↑ RBF and diuresis.

Indications and doses:

Respiratory uses: management of asthma and bronchospasm:

- Acute bronchial asthma: aminophylline is given by **slow i.v. infusion** 250 mg i.v. (at least over 15 minutes to avoid syncope or cardiac arrest), followed by maintenance i.v infusion of 0.7 mg/kg/h.
- Chronic bronchial asthma: as a prophylactic treatment. Sustained release tablets of theophylline 100-300 mg/day or rectal suppository of aminophylline can be given.
- Status asthmaticus and patients refractory to adrenergic agents.

CNS uses:

- Treatment of CNS depression due to various causes.
- To delay physical fatigue.
- Treatment of migraine (caffeine + ergotamine): to increase VC of cerebral blood vessels and increase absorption of ergotamine from GIT.

CVS uses:

- Acute pulmonary edema due to acute left sided HF.
- Refractory cases of congestive heart failure (they are +ve inotropic)
- Neonatal apnea syndrome.

GIT uses: acute biliary colic.

Side effects:

- **CNS:** irritability, headache, insomnia, nervousness and convulsions.

- **CVS:** palpitations, tachycardia, and arrhythmias. **Rapid i.v. injection** can cause hypotension, syncope and **cardiac arrest.**
- **GIT:** nausea, vomiting, anorexia, **hyperacidity** and reactivation of peptic ulcer.

Precautions:

- Aminophylline must be given by slow i.v.i. (at least over 15 minutes to avoid sudden syncope or cardiac arrest).
- Used with caution in severe cardiac disease, severe hypoxemia, and renal and hepatic disease and in elderly and neonates.
- They should not be given to patients with peptic ulcer.

Drug interactions:

- Enzyme inhibitors (cimetidine and erythromycin) → ↑ serum levels of methylxanthines and ↑ their toxicity (arrhythmia).
- Enzyme inducers (smoking, rifampin) → ↓ their serum levels and reduce their effect.

N.B: There is increased risk of **arrhythmia** when using both B2 agonist and xanthines in the same time because both drugs are arrhythmogenic.

Reduction of bronchial inflammation and hyperreactivity

1. Corticosteroids:

Mechanism of action:

1. They inhibit antigen-antibody reaction.
2. They inhibit T cell and macrophages proliferation and activation.
3. They inhibit inflammatory cell infiltration of the bronchi and ↓ cytokine release.
4. They inhibit PGs and LTs synthesis through inhibition of phospholipase A_2 enzyme.
5. Stabilize lysosomal membranes and ↓ capillary permeability.
6. Potentiate the effect of endogenous catecholamines and up-regulation of β receptors.

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Why NSAIDs can not be given in bronchial asthma?

Because NSAIDs inhibit *Cox* enzyme but NOT *lipooxygenase* enzyme leading to accumulation of LTs which are potent bronchoconstrictors.

Indications and doses:

- Acute bronchial asthma: by i.v. injection or inhalation (**beclomethazone**).
- Chronic bronchial asthma: **prednisolone** 20 mg/d or **dexamethazone** 4-8 mg/d.
- Severe asthma and status asthmaticus: **hydrocortisone** 200 mg is given i.v. every 4 hrs until improvement followed by maintenance oral therapy.
- **Inhaled corticosteroids (e.g. beclomethazone):** should be considered the 1st choice in newly diagnosed asthma. They have the following advantages:
  - Their efficacy is equal to inhaled β_2 agonists.
  - Minimal systemic side effects.

Adverse effects:

- **If used systemic:** .....see endocrine chapter.
- **If used by inhalation:** they cause **oropharyngeal candidiasis.** It could be avoided by:
  - Mouth wash and gargle after each inhalation.
  - If candida infection occurred, it must be treated by **nystatin mouthwash** or **amphotricin-B lozenges.**

Precautions:

- They must be **withdrawn gradually** to avoid acute Addisonian crisis.
- Diet should be rich in K^+ and proteins and low in NaCl and carbohydrates.
- **Continuous check** for any increase in weight, edema, sugar in urine or BP.
- If the patient develops **acute infection**, he must be treated by adequate antibiotics with decreased dose of steroid.

2 Leukotriene inhibitors:

Zafirlukast and montelukast:

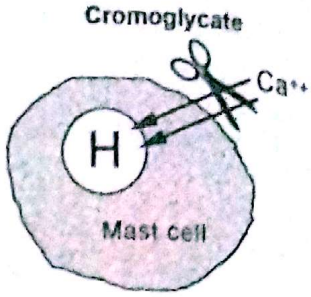
- They **block leukotriene receptors.**
- Zafirlukast it is given twice daily but Montelukast is given once daily.
- **Uses:** treatment of *bronchial asthma* and other inflammatory diseases.

Zileuton:

- It **inhibits 5-lipooxygenase enzyme → ↓ leukotriene synthesis.**
- **Uses:** treatment of *bronchial asthma*.

Prophylactic treatment: Mast cell stabilizers

1. Sodium cromoglycate (Cromolyn; Intal)



It is poorly absorbed drug. It is given as micronized powder through a spinhaler.

Mechanism of action:

It inhibits mast cell degranulation by decreasing Ca^{2+} influx across cell membrane → ↓ histamine release.

Therapeutic uses:

- **Prophylactic treatment** in chronic asthma: by inhalation in-between the attacks.
- Allergic rhinitis and hay fever.
- Allergic conjunctivitis: Cromolyn eye drops.
- Ulcerative colitis and Crohn's disease: oral capsules.

N.B.

Mast cell stabilizers are not given during the acute attack. If given during the acute attacks, they may aggravate bronchospasm.

Side effects: side effects occur at site of administration:

- Local irritation: throat irritation, cough, and chest tightness.
- Bronchospasm: (prevented by inhaling β_2 agonist before cromolyn inhalation).

2. Ketotifen (Zaditen)

Similar to cromolyn but: (1) Has antihistaminic action, and (2) Given orally.

Uses: the same as sodium cromoglycate.

Side effects: atropine-like action: sedation, dry mouth and dizziness.

3. Nedocromil: Similar to cromoglycate but more potent.

Prevention of exposure to precipitating factors

- Avoid exposure to the causative antigen.
- Treat respiratory infection.
- Avoid **drugs that induce bronchoconstriction** e.g.

- Cholinomimetic drugs.
- Non-selective β- blockers.
- Histamine releasers e.g. morphine, trimetaphan, curare, penicillins.
- Bronchoconstrictor prostaglandins e.g. $PGF_{2\alpha}$
- Aspirin and other NSAIDs (they ↑ synthesis of leukotrienes).

Other drugs used in treatment of bronchial asthma

- **Expectorants and mucolytics:** reduce mucus viscosity.
- **Mixture of oxygen (20%) and helium (80%):**
  - Helium is an inert gas. Its low density facilitates O_2 diffusion through obstructed airways → ↓ work of breathing.
  - Inhalation of mixture of helium and O_2 is indicated in severe cases of acute bronchial asthma and status asthmaticus.

N.B. Antihistamines are not used in bronchial asthma because:
- Bronchospasm is due to multiple mediators and not only due to histamine.
- They have atropine-like action → dryness of bronchial secretion, which become difficult to expel.

Treatment of acute severe asthma (status asthmatics)

Definition: acute severe asthma (status asthmatics) is a condition in which bronchodilators are ineffective in relieving the attack after 24 hours.

Management:
1. Hospitalization.
2. Perform chest X-ray, ECG and blood samples for electrolytes.
3. **Oxygen:** humidified O_2 or O_2-Helium mixture.
4. **β_2 agonists:** by inhalation.
5. **Hydrocortisone:** 200 mg i.v. / 6hs.
6. **Aminophylline:** 500 mg slowly i.v.
7. **Mucolytics** and expectorants e.g. bromohexine.
8. **Antibiotics** e.g. amoxycillin 500 mg /8hs.
9. Correction of acidosis and dehydration **5% glucose**

Part 3: Pharmacology of oxygen

Types of oxygen:

- **Pure oxygen:** oxygen is available as compressed gas in steel cylinders.
- **Mixtures of oxygen:** oxygen can be given in mixture with CO_2 or helium.
- **Humidified oxygen:** oxygen can be given under water sealing to prevent irritation of respiratory tract.
- **Hyperbaric oxygen:** oxygen under pressure.

Therapeutic uses of oxygen:

- Correction of hypoxia:
  a. Inadequate pulmonary **ventilation** due to:
     - Airway obstruction: e.g. bronchospasm.
     - Muscle weakness: e.g. in CNS diseases, NMB, and anesthetics.
     - Pulmonary disease: e.g. pneumonia and pulmonary edema.
  b. Inadequate **delivery** of oxygen to tissues: e.g. in shock, acute MI.
  c. Inadequate **utilization** of O_2 by tissue: e.g. in cyanide poisoning.
  d. Inadequate O_2 **content** of the atmospheres.
- During anesthesia as a carrier for gaseous and volatile anesthetics.
- Hyperbaric oxygen: (O_2 under pressure):
  - Decompression sickness and with air embolism.
  - Chronic refractory osteomyelitis, anaerobic infection e.g. gas gangrene, crush injury and tissue graft.
  - Treatment of generalized hypoxia in carbon monoxide poisoning

Methods of administration:

- Nasal cannula, masks, head tents, oxygen tents and endotracheal tubes.
- Hyperbaric oxygen is given in pressure chamber of O_2.

Dangers, adverse effects and precautions:

- Fire and explosions: (do not light cigarette or fire beside it).
- Irritation of nose, pharynx and trachea: (give humidified O_2).
- Inhibition of mucociliary function → ↓ tracheal outflow of mucous.
- Respiratory depression:

- In some cases of partial respiratory depression (e.g. in head injuries, barbiturates, etc.), there is hypoxia and hypercapnea (excess CO_2).
- The excess CO_2 leads to more RC depression (CO_2 narcosis) and hypoxia becomes the only stimulus for RC.
- If pure O_2 was administered, hypoxia is corrected and the patient develops apnea due to complete RC depression.
  - ▶ How to avoid? Give carbogen instead of pure O_2 (see below).

Retrolental fibroplasias: high concentration of O_2 in neonates stimulates fibrous tissue formation posterior to the eye lens and permanent blindness. So, O_2 should be used only when needed and its concentration must not exceed 35-40% in premature infants.

Pulmonary oxygen toxicity: high conc of O_2 may lead to pulmonary fibrosis.

High-pressure nervous syndrome: hyperbaric O_2 can cause toxic CNS effects e.g. muscular twitching, visual symptoms, mood changes, nausea and vomiting, loss of consciousness and generalized convulsions.

Ebrahim said behairy

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- وده كله آخر برانش

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