BP602T. PHARMACOLOGY-III (THEOTY)

UNIT-I

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UNIT-I **10hours**

1. Pharmacology of drugs acting on Respiratory system

a. Anti -asthmatic drugs

b. Drugs used in the management of COPD

c. Expectorants and antitussives

d. Nasal decongestants

e. Respiratory stimulants

2. Pharmacology of drugs acting on the Gastrointestinal Tract

a. Antiulcer agents.

b. Drugs for constipation and diarrhoea.

c. Appetite stimulants and suppressants.

d. Digestants and carminatives.

e. Emetics and anti-emetics.

DRUGS ACTING ON RESPIRATORY SYSTEM

DRUGS USED IN COUGH:

Introduction:

Cough is a protective reflex which helps in expulsion of respiratory secretion or foreign particles which are irritant to the respiratory tract. Irritation to any part of respiratory tract starting from pharynx to lungs carried impulses by afferent fibres in vagus and sympathetic nerve to the cough centre in the medulla oblongata. Cough may be **dry** (without sputum or unproductive) or **productive** (with sputum production). There are certain factors which are responsible for production of cough e.g.

i) *Environmental factors:* Certain irritant pollutants, dust, smoking, automobile smoke.

ii) Upper respiratory tract infection.

iii) Acute lung infections, asthma and certain pleural diseases e.g. pleural effusion.

iv) Chronic pulmonary ailments e.g. tuberculosis, chronic bronchitis & lung cancer etc.

v) Drug induced cough (e.g. with the use of ACE inhibitors).

The drugs and their combination used in cough are discussed below.

1. *Pharyngeal demulcents*: Lozenges, cough drops, linctuses containing syrup, glycerine, liquorice.

2. *Expectorants (Mucokinetics):*

(a) *Bronchial secretion enhancers:* Sodium or Potassium citrate, Potassium iodide, Guaiphenesin (Glyceryl guaiacolate), balsum of Tolu, Vasaka, Ammonium chloride.

(b) *Mucolytics:* Bromhexine, Ambroxol, Acetyl cysteine, Carbocisteine

3. *Antitussives (Cough centre suppressants)*

(a) ***Opioids:*** Codeine, Ethylmorphine, Pholcodeine.

(b) ***Nonopioids:*** Noscapine, Dextromethorphan, Chlophedianol.

(c) ***Antihistamines:*** Chlorpheniramine, Diphenhydramine, Promethazine.

(d) ***Peripherally acting:*** Prenoxdiazine.

4. *Adjuvant antitussives:*

Bronchodilators: *Salbutamol, Terbutalin.*

Pharyngeal Demulcents:

These are the agents which are generally administered in the form of lozenges, cough drops and cough linctus. They produce the soothing action on throat directly and by increasing the flow of saliva and provide symptomatic relief from dry cough.

Expectorant:

Expectorants are the drugs which increase the production of bronchial secretion and reduce its viscosity to facilitate its removal by coughing. Expectorants can stimulate the expulsion of respiratory secretion either directly or reflexly. Certain volatile oils of plant origin such as oil of lemon, anise, eucalyptus by steam inhalation route increase the respiratory secretion by its direct action. Another compound, syrup tolu (Tolu balsum) directly increase bronchial secretion.

The second type is reflex expectorant, which acts by stimulating the gastric reflexes which help to increase the respiratory secretions. Certain salts which are used as emetics, when used in sub emetic dose, increase the bronchial secretion and expel it out, they are known as **saline expectorants**.

Ammonium salts (as chloride and carbonate) are gastric irritant in nature and reflexly increase bronchial secretion.

Potassium salts (as iodide) act by both direct action and reflexly to increase the respiratory secretions and decrease its viscosity thus they are easy to expel out. Potassium iodide is generally used for cough associated with chronic bronchitis and asthma but it interferes with thyroid function tests, so it is dangerous in patients sensitive to iodine and chronic use can induce hypothyroidism and goitre.

Sodium and **potassium citrate** and **acetate** act by increasing bronchial secretion by their salt actions. Certain alkaloids such as **vasicine** obtained from plant *Adhatoda vasica* act as potent expectorant and mucolytic agent. **Bromhexine**, a derivative of vasicine depolymerises mucopolysaccharides directly and by liberating lysosomal enzymes. Another compound **acetylcysteine** opens disulfide bonds in mucoproteins present in sputum and decrease its viscosity. **Carbocisteine** acts in same manner.

Antitussives:

They are central cough suppressants and act centrally to raise the threshold of cough centre and inhibit the cough reflex by suppressing the coordinating cough centre in the medulla oblongata. They are mainly used in dry (unproductive) cough and are ineffective in cough due to pleural disease.

Codeine, which is an opium alkaloid is most commonly used as antitussive and is more selective for cough centre. Like morphine, it depresses cough centre but is less constipating and abuse liability is low. It is relatively safe drug used in cough along with analgesic property and it's only important adverse effect is constipation.

Pholcodeine is similar to codeine in efficacy and is longer acting. It has no analgesic or addicting property.

Noscapine is another opium alkaloid of benzylisoquinoline group. It is used as antitussive with no analgesic and drug abuse or drug dependence property. It is contraindicated in asthmatic patients as it releases histamine which can cause bronchoconstriction.

Dextromethorphan is a synthetic compound and is used as antitussive and is as effective as codeine without any addiction liability.

Pipazethate is another synthetic compound of phenothiazine category used as antitussive with little analgesic and sedative properties.

Antihistaminics:

Many H1 antihistaminics have been added to antitussive/expectorant formulations. They do not act on cough centre but provide relief due to their sedative and anticholinergic action.

Bronchodilators:

Bronchodilators are helpful in individuals with cough and bronchoconstriction due to bronchial hyper-reactivity. They help by improving the effectiveness of cough in clearing secretions.

ANTIASTHMATIC DRUGS

Introduction:

Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to a variety of stimuli and manifests as narrowing of the airways that change in severity either spontaneously or as a result of therapy. The impairment of air flow in asthma is caused by three abnormalities:

a) Constriction of bronchial smooth muscle (bronchoconstriction).

b) Swelling of bronchiolar mucosa (bronchial edema).

c) Excessive bronchial secretions.

Drugs used in management of bronchial asthma are discussed according to their main groups.

CLASSIFICATION:

I. *Bronchodilators*

A. β*2 Sympathomimetics:* Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol, Ephedrine.

B. *Methylxanthines:* Theophylline (anhydrous), Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Theophylline ethanolate of piperazine, Doxophylline.

C. *Anticholinergics:* Ipratropium bromide, Tiotropium bromide.

II. *Leukotriene antagonists* : Montelukast, Zafirlukast.

III. *Mast cell stabilizers:* Sodium cromoglycate, Ketotifen.

IV. *Corticosteroids:*

A. *Systemic:* Hydrocortisone, Prednisolone and others.

B. *Inhalational:* Beclomethasone dipropionate, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide.

V. *Anti-IgE antibody**:*** Omalizumab

Sympathomimetics:

β_2-agonists are invariably used in the symptomatic treatment of asthma. Epinephrine and ephedrine are structurally related to the catecholamine norepinephrine, a neurotransmitter of the adrenergic nervous system. B_2- agonists are the drug of choice to relieve acute exacerbation of asthma and prevent bronchoconstriction following exercise or other stimuli. After inhalation the β_2-agonists have rapid onset of action (within minutes), but are active only for 4 to 6 hours. The detailed pharmacology is discussed in chapter 'Adrenergic Agents'.

Salbutamol is a highly selective β_2-adrenergic stimulant having a prominent bronchodilator action. It is given by oral as well as inhalation route by nebulizer. Palpitation, restlessness, nervousness are the common side effects with salbutamol.

Terbutaline is similar to salbutamol and is administered by oral, parenteral as well as inhalational route.

Salmeterol is a newer long acting selective alpha2 adrenergic agonist with slow onset of action, used for maintenance therapy in asthma, nocturnal asthma and asthma induced by exercise.

Methylxanthines (Theophylline and its Derivatives)

Among the methylxanthines, aminophylline is most commonly used drug in the treatment of bronchial asthma. It is a stable mixture of theophylline and ethylenediamine. These drugs inhibit the enzyme phosphodiesterase, this inhibition results in higher concentration of intracellular cyclic AMP. Increased cAMP leads to bronchodilatation, cardiac stimulation and vasodilatation.

Other important methylxanthines are caffeine and theobromine. Caffeine and theophylline are pharmacologically CNS stimulants and produce alertness and cortical arousal, but in higher doses causes restlessness, nervousness and insomnia. Methylxanthines stimulate the heart and increase the force of myocardial contraction. They relax smooth muscles especially bronchi in asthmatic patients.

Anticholinergics:

Anticholinergics, like atropine and its derivative ipratropium bromide blockcholinergic pathways that cause airway constriction. They may provide added bronchodilator effect in patients who are receiving beta2-adrenergic agents for asthma.

The detailed pharmacology is discussed in chapter 'Cholinergic blocking agents.'

Mast Cell Stabilizers:

The important members in this group are sodium chromoglycate and ketotifen. They are highly effective in preventing asthma attacks. They inhibit degranulation of mast cells. These agents do not produce bronchodilatation and also do not antagonize the constrictor effect of histamine etc. Therefore they are not beneficial in acute attacks of asthma and are used for prophylaxis only.

Sodium cromoglycate is not absorbed orally and is administered by aerosol. The most important therapeutic uses of mast cell stabilizers is the prophylaxis

of bronchial asthma, treatment of nasal congestion and chronic allergic conjunctivitis.

Corticosteroids:

Like mast cell stabilizer, corticosteroids do not relax airway smooth muscle directly but reduce bronchial reactivity, increase airway caliber, suppress inflammatory response to antigen antibody reaction or trigger stimuli and reduce the frequency of asthma exacerbations. They produce more

sustained symptomatic relief than any bronchodilator and mast cell stabilizer. Systemic steroids are used in both severe chronic asthma and in acute emergency of asthma (*status asthmaticus*).

The inhaled steroids suppress asthma by a topical anti-inflammatory action without causing any systemic side effects. They reduce the bronchial hyperreactivity and increase the peak expiratory flow rate in asthmatic patients. They are not effective during an acute attack or in status asthmaticus. Side effects are sore throat, hoarseness of voice, dysphonia, oropharyngeal candidiasis.

Leukotriene Pathway Inhibitors:

Apart from histamine, leukotrienes liberated during inflammation are more powerful bronchoconstrictor and are longer acting. Leukotrienes also increase bronchial mucus secretion, increase vascular permeability, bronchoconstriction and increased bronchial reactivity. All the leukotrienes are derived from 5- lipoxygenase pathway of arachidonic acid and are synthesized by a variety of inflammatory cells in the airways e.g. eosinophils, mast cells, basophils and macrophages. The drug, **montelukast** and **zafirlukast** are available for the treatment of asthmatic patients.

NASAL DECONGESTANTS:

These are α agonists which on topical application as dilute solution (0.05–0.1%) produce local vasoconstriction. The imidazoline compounds- naphazoline, xylometazoline and oxymetazoline are relatively selective α2 agonist (like clonidine). They have a longer duration of action (12 hours) than ephedrine. They may cause initial stinging sensation (specially naphazoline). Regular use of these agents for long periods should be avoided because mucosal ciliary function is impaired: atrophic rhinitis and anosmia can occur due to persistent vasoconstriction. They can be absorbed from the nose and produce systemic effects, mainly CNS depression and rise in BP. These drugs should be used cautiously in hypertensives and in those receiving MAO inhibitors.

Pseudophedrine: A stereoisomer of ephedrine; causes vasoconstriction, especially in mucosae and skin, but has fewer CNS and cardiac effect and is a poor bronchodilator (little β2 agonistic activity). It has been used orally as a decongestant of upper respiratory tract and nose. Combined with antihistaminics, mucolytics, antitussives and analgesics, it is believed to afford symptomatic relief in common cold, allergic rhinitis, and upper respiratory tract infections.

Phenylpropanolamine (PPA): Being chemically and pharmacologically similar to ephedrine, PPA causes vasoconstriction and has some amphetamine like CNS effects, including suppression of hunger. It was included in a large number of oral cold/decongestant combination remedies, and in USA it was used as an appetite suppressant as well. Following reports and case control studies associating PPA use with haemorrhagic stroke and concerns regarding its potential to precipitate behavioural/psychiatric disturbances, many countries, led by USA, prohibited the sale of PPA containing medicines decades back.

ANALEPTICS (Respiratory stimulants):

These are drugs which stimulate respiration and can have resuscitative value in coma or fainting. They do stimulate respiration in subconvulsive doses, but margin of safety is narrow; the patient may get convulsions while still in coma. Mechanical support to respiration and other measures to improve circulation are more effective and safe. The role of analeptics in therapeutics is very limited. Situations in which they may be employed are:

(a) As an expedient measure in hypnotic drug poisoning until mechanical ventilation is instituted.

(b) Suffocation on drowning, acute respiratory insufficiency.

(c) Apnoea in premature infant.

(d) Failure to ventilate spontaneously after general anaesthesia.

However, the overall utility of analeptics is dubious.

Doxapram It acts by promoting excitation of central neurones. At low doses it is more selective for the respiratory centre than other analeptics. Respiration is stimulated through carotid and aortic body chemoreceptors as well. Falling BP rises. Continuous i.v. infusion of doxapram may abolish episodes of apnoea in premature infant not responding to theophylline.

DRUGS ACTING ON THE GASTROINTESTINAL TRACT

Antiulcer agents

PEPTIC ULCER: Peptic ulcer occurs in that part of the gastrointestinal tract (g.i.t.) which is exposed to gastric acid and pepsin, i.e. the stomach and duodenum. The etiology of peptic ulcer is not clearly known. It results probably due to an imbalance between the *aggressive* (acid, pepsin, bile and *H. pylori*) and the *defensive* (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, high mucosal blood flow, innate resistance of the mucosal cells) factors. A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of *Helicobacter pylori* infection as a contributor to ulcer formation and recurrence has been recognized.

Classification of antiulcer drugs:

1. *Reduction of gastric acid secretion*

(a) *H2 antihistamines*: Cimetidine, Ranitidine, Famotidine, Roxatidine

(b) *Proton pump inhibitors*: Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Dexrabeprazole

(c) *Anticholinergic drugs*: Pirenzepine, Propantheline, Oxyphenonium

(d) *Prostaglandin analogue:* Misoprostol

2. *Neutralization of gastric acid (Antacids)*

(a) *Systemic:* Sodium bicarbonate, Sod. citrate

(b) *Nonsystemic:* Magnesium hydroxide, Mag. trisilicate, Aluminium hydroxide gel, Magaldrate, Calcium carbonate

3. *Ulcer protectives:* Sucralfate, Colloidal bismuth subcitrate (CBS)

4. *Anti-H. pylori drugs:* Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

H2 ANTAGONISTS:

These are the first class of highly effective drugs for acid-peptic disease, but have been surpassed by proton pump inhibitors (PPIs). Four H2 antagonists cimetidine, ranitidine, famotidine and roxatidine are available in India.

Pharmacological actions:

1. *H2 blockade:* Cimetidine and all other H2 antagonists block histamine-induced gastric secretion, cardiac stimulation (prominent in isolated preparations, especially in guinea pig), uterine relaxation (in rat) and bronchial relaxation (H2 blockers potentiate histamine induced bronchospasm).

2. *Gastric secretion:* The only significant *in vivo* action of H2 blockers is marked inhibition of gastric secretion. All phases (basal, psychic, neurogenic, gastric) of secretion are suppressed dose-dependently. Secretary responses to not only histamine but all other stimuli (ACh, gastrin, insulin, alcohol, food) are attenuated. The volume, pepsin content and intrinsic factor secretion are reduced, but the most marked effect is on acid. The usual ulcer healing doses produce 60–70% inhibition of 24 hr acid output. The H2 blockers have antiulcerogenic effect. Gastric ulceration due to stress and drugs (NSAIDs, cholinergic, histaminergic) is prevented. They do not have any direct effect on gastric or esophageal motility or on lower esophageal sphincter (LES) tone.

Pharmacokinetics:

Cimetidine is adequately absorbed orally, though bioavailability is 60–80% due to first pass hepatic metabolism. Absorption is not interfered by presence of food in stomach. It crosses

placenta and reaches milk, but penetration in brain is poor because of its hydrophilic nature. About 2/3 of a dose is excreted unchanged in urine and bile, the rest as oxidized metabolites. The elimination t½ is 2–3 hr.

Adverse effects:

Cimetidine is well tolerated by most patients: adverse effects occur in < 5%. These are generally mild.

• Headache, dizziness, bowel upset, dry mouth, rashes.

• Cimetidine (but not other H2 blockers) has antiandrogenic action (displaces dihydrotestosterone from its cytoplasmic receptor), increases plasma prolactin and inhibits degradation of estradiol by liver. High doses given for long periods have produced gynaecomastia, loss of libido, impotence and temporary decrease in sperm count.

• Transient elevation of plasma aminotransferases; but hepatotoxicity is rare.

Ranitidine: A nonimidazole (has a furan ring) H2 blocker, it has several desirable features compared to cimetidine:

• About 5 times more potent than cimetidine. Though its pharmacokinetic profile and t½ of 2–3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency.

• No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism—no effect on male sexual function or gynaecomastia.

• Lesser permeability into the brain: lower propensity to cause CNS effects. In fact, little effect outside g.i.t. has been observed.

• Overall incidence of side effects is lower: headache, diarrhoea/constipation, dizziness have an incidence similar to placebo.

Uses:

The H2 blockers are used in conditions in which it is profitable to suppress gastric acid secretion. Used in appropriate doses, all available agents have similar efficacy.

1. *Duodenal ulcer*
2. *Gastric ulcer*
3. *Stress ulcers and gastritis*
4. *Zollinger-Ellison syndrome*
5. *Gastroesophageal reflux disease (GERD)*

PROTON PUMP INHIBITORS (PPIs):

Omeprazole: It is the prototype member which inhibits the final common step in gastric acid secretion. The PPIs have overtaken H2 blockers for acid-peptic disorders. The only significant pharmacological action of omeprazole is dose dependent suppression of gastric acid secretion; without anticholinergic or H2 blocking action. It is a powerful inhibitor of gastric acid: can totally abolish HCl secretion, both resting as well as that stimulated by food or any of the secretagogues, without much effect on pepsin, intrinsic factor, juice volume and gastric motility. Omeprazole is inactive at neutral pH, but at pH < 5 it react covalently with H+K+ATPase enzyme and inactivate it irreversibly, especially when two molecules of omeprazole react with one molecule of the enzyme. Acid secretion resumes only when new H+K+ATPase molecules are synthesized (reactivation half time 18 hours).

Pharmacokinetics: All PPIs are administered orally in enteric coated form to protect them from molecular transformation in the acidic gastric juice. The e.c. tablet or granules filled in capsules should not be broken or crushed before swallowing. Oral bioavailability of omeprazole

is ~50% due to acid lability. Bioavailability of all PPIs is reduced by food; they should be taken in empty stomach, followed 1 hour later by a meal to activate the H+K+ ATPase and make it more susceptible to the PPI. Omeprazole is highly plasma protein bound, rapidly metabolised in liver (plasma t½ ~1 hr). The metabolites are excreted in urine.

Uses:

1. *Peptic ulcer:*

2. *Bleeding peptic ulcer:*

3. *Stress ulcers:*

4. *Gastroesophageal reflux disease (GERD)*

5. *Zollinger-Ellison syndrome*

Adverse effects*:* PPIs produce minimal adverse effects. Nausea, loose stools, headache, abdominal pain, muscle and joint pain, dizziness are complained by 3–5%. Rashes (1.5% incidence), leucopenia and hepatic dysfunction are infrequent. No harmful effects of PPIs during pregnancy are known.

Pantoprazole: It is similar in potency and clinical efficacy to omeprazole, but is more acid stable and has higher oral bioavailability. It is also available for i.v. administration; particularly employed in bleeding peptic ulcer and for prophylaxis of acute stress ulcers. Affinity for cytochrome P450 is lower than omeprazole or lansoprazole: risk of drug interactions is minimal.

Rabeprazole: This newer PPI is claimed to cause fastest acid suppression. Due to higher pKa, it is more rapidly converted to the active species. However, potency and efficacy are similar to omeprazole.

PROSTAGLANDIN ANALOGUE:

PGE2 and PGI2 are produced in the gastric mucosa and appear to serve a protective role by inhibiting acid secretion and promoting mucus as well as $HCO3^{-}$ secretion. In addition, PGs inhibit gastrin release, increase mucosal blood flow and probably have an "cytoprotective" action. However, the most important to be their ability to reinforce the mucus layer covering gastric and duodenal mucosa.

Natural PGs have very short t½. *Misoprostol* is a longer acting synthetic PGE1 derivative which inhibits acid output dose dependently. However, reduction in 24 hour acid production is less than H2 blockers because of shorter duration of action (~3 hr.) Ulcer healing rates comparable to cimetidine have been obtained in 4–8 weeks, but misoprostol is poorer in relieving ulcer pain. Some patients may even complain of increased pain during the first week of therapy.

Adverse effects: Major problems in the use of misoprostol are—diarrhoea, abdominal cramps, uterine bleeding, abortion, and need for multiple daily doses. Patient acceptability is poor.

Uses: The primary indication of misoprostol is the prevention and treatment of NSAID associated gastrointestinal injury and blood loss. However, it is seldom employed now because PPIs are more effective, more convenient, better tolerated and cheaper.

ANTACIDS:

These are basic substances which neutralize gastric acid and raise pH of gastric contents. Antacids do not decrease acid production. The potency of an antacid is generally expressed in terms of its *acid neutralizing capacity* (ANC), which is defined as number of mEq of 1N HCl that are brought to pH 3.5 in 15 min (or 60 min in some tests) by a unit dose of the antacid preparation. This takes into consideration the rate at which the antacid dissolves and reacts with

HCl. This is important because a single dose of any antacid taken in empty stomach acts for 30–60 min only, since in this time any gastric content is passed into duodenum. Taken with meals antacids may act for at the most 2–3 hr.

Systemic Antacids:

Sodium bicarbonate: It is water soluble, acts instantaneously, but the duration of action is short. It is a potent neutralizer, pH may rise above 7. However, it has several demerits:

(a) Absorbed systemically: large doses will induce alkalosis.

(b) Produces CO2 in stomach → distention, discomfort, belching, risk of ulcer perforation.

(c) Increases Na+ load: may worsen edema and CHF.

Use of sod. bicarbonate is restricted to casual treatment of heartburn. It provides quick symptomatic relief. Other uses are to alkalinize urine and to treat acidosis.

Nonsystemic Antacids:

Mag. hydroxide has low water solubility: its aqueous suspension (milk of magnesia) has low concentration of OH^- ions and thus low alkalinity. However, it reacts with HCl promptly and is an efficacious antacid (1 g → 30 mEq HCl). Rebound acidity is mild and brief. MILK OF MAGNESIA 0.4 g/5 ml suspension: 5 ml neutralizes 12 mEq acid.

Magnesium trisilicate has low solubility and reactivity; 1 g can react with 10 mEq acid, but in clinical use only about 1 mEq is neutralized. About 5% of administered Mg is absorbed systemically— may cause problem if renal function is inadequate. All Mg salts have a laxative action by generating osmotically active MgCl2 in the stomach and through Mg2+ ion induced cholecystokinin release. Soluble Mg salts are used as osmotic purgatives.

Aluminium hydroxide gel It is a bland, weak and slowly reacting antacid. On keeping it slowly polymerizes to variable extents into still less reactive forms. Thus, the ANC of a preparation

gradually declines on storage. Also, the product from different manufacturers may have differing ANCs; usually it varies from 1–2.5 mEq/g. Thus, 5 ml of its suspension may neutralize just 1 mEq HCl. As such, little worthwhile acid neutralization is obtained at conventional doses. use.

Magaldrate It is a hydrated complex of hydroxymagnesium aluminate that initially reacts rapidly with acid and releases alum. hydrox. which then reacts more slowly. It is a good antacid with prompt and sustained neutralizing action.

Calcium carbonate It is a potent and rapidly acting acid neutralizer (1 g → 20 mEq HCl), but ANC of commercial preparations is less and variable due to differing particle size and crystal structure. Though it liberates CO2 in the stomach at a slower rate than NaHCO3, it can cause distention and discomfort. The Ca2+ ions are partly absorbed.

Uses: Antacids are no longer used for healing peptic ulcer, because they are needed in large and frequent doses, are inconvenient, can cause acid rebound and bowel upset and have poor patient acceptability. Antacids are now employed only for intercurrent pain relief and acidity, mostly self-prescribed by the patients as over the counter preparations.

ULCER PROTECTIVES:

Sucralfate: It is a basic aluminium salt of sulfated sucrose. Sucralfate polymerizes at pH < 4 by cross linking of molecules, assuming a sticky gel-like consistency. It preferentially and strongly adheres to ulcer base, especially duodenal ulcer; has been seen endoscopically to remain there for ~ 6 hours. Surface proteins at ulcer base are precipitated, together with which it acts as a physical barrier preventing acid, pepsin and bile from coming in contact with the ulcer base. Dietary proteins get deposited on this coat, forming another layer. Sucralfate has no acid neutralizing action, but delays gastric emptying—its own stay in stomach is prolonged.

Sucralfate is minimally absorbed after oral administration. Its action is entirely local. It promotes healing of both duodenal and gastric ulcers. Healing efficacy has been found similar to cimetidine at 4 weeks.. However, sucralfate is infrequently used now because of need for 4 large well-timed daily doses and the availability of simpler and more effective H2 blockers/PPIs.

Dose: The ulcer healing dose of sucralfate is 1 g taken in empty stomach 1 hour before the 3 major meals and at bed time for 4–8 weeks.

Colloidal bismuth subcitrate (CBS):

It is a colloidal bismuth compound; water soluble but precipitates at pH < 5. It is not an antacid but heals 60% ulcers at 4 weeks and 80–90% at 8 weeks. The mechanism of action of CBS is not clear; probabilities are:

• May increase gastric mucosal PGE2, mucus and HCO_3^- production.

• May precipitate mucus glycoproteins and coat the ulcer base.

• May detach and inhibit *H.pylori* directly.