RecNotes

GASTROINTESTINAL AGENTS

Glands of the Stomach

The stomach is divided into three functional areas, each with specific glands.

- Cardiac zone (uppermost area of the stomach) contains the cardiac glands
- Pyloric zone (lowermost part of the stomach) contains the pyloric glands
- The greater part of the body of the stomach, the fundus, contains the gastric glands.

The gastric glands play the most significant role in acid-related disorders.

Cells of the Gastric Gland

Parietal cells

- Produce and secrete HCl
- Primary site of action for many acid-controller drugs

Hydrochloric Acid

- Secreted by the parietal cells/oxyntic cells when stimulated by food
- Maintains stomach at pH of 1 to 4
- Secretion also stimulated by:

Large fatty meals

Excessive amounts of alcohol

Emotional stress

Classification of inorganic gastrointestinal agents :

1. Products for altering gastric pH
2. Protectives for intestinal inflammation
3. Adsorbents for intestinal toxins
4. Cathartics or laxatives for inflammation

Products for altering gastric pH

- **Acidifying agents**
- **Antacids**

Agents used to increase the stomach pH is known as acidifying agents.
e.g. Ammonium chloride, Calcium chloride, dilute HCl etc. can be used to treat Achlorhydria.

Achlorhydria is the absence of hydrochloric acid in the gastric secretions.
Patients with this condition fall into two categories:

- Those who remain free of gastric HCL after stimulation with histamine phosphate (patients with subtotal gastrectomy, atrophic gastritis, carcinoma of the stomach or stomach polyps).
- Those who normally lack gastric HCL but respond to stimulation by histamine (patients with chronic nephritis, chronic alcoholism, tuberculosis, hyperthyroidism, pellagra).

Functions of HCl:

- kills the bacteria in ingested food and drink,
- softens fibrous foods
- promotes the formation of pepsin that helps in digestion

Thus lack of HCl can cause gastrointestinal disturbances.

Symptoms of Achlorhydria:

- mild diarrhea or frequent bowel movements
- epigastric (upper middle portion of the abdomen) pain
- sensitivity to spicy foods

Treatment :

Diluted Hydrochloric Acid N.F (the usual 5ml dose of Diluted Hydrochloric acid N.F. added to 200 ml of water provides about 15mEQ of acid).

Antacids

- Antacids are drugs that are widely used to relief heartburn , uncomfortable feeling from overeating, and dyspepsia (indigestion) and other non-specific GI symptoms.

- Antacids can neutralize the excess gastric hydrochloric acid (by reacting with the acid and forming salt and water) which may be causing pain and possible ulceration.

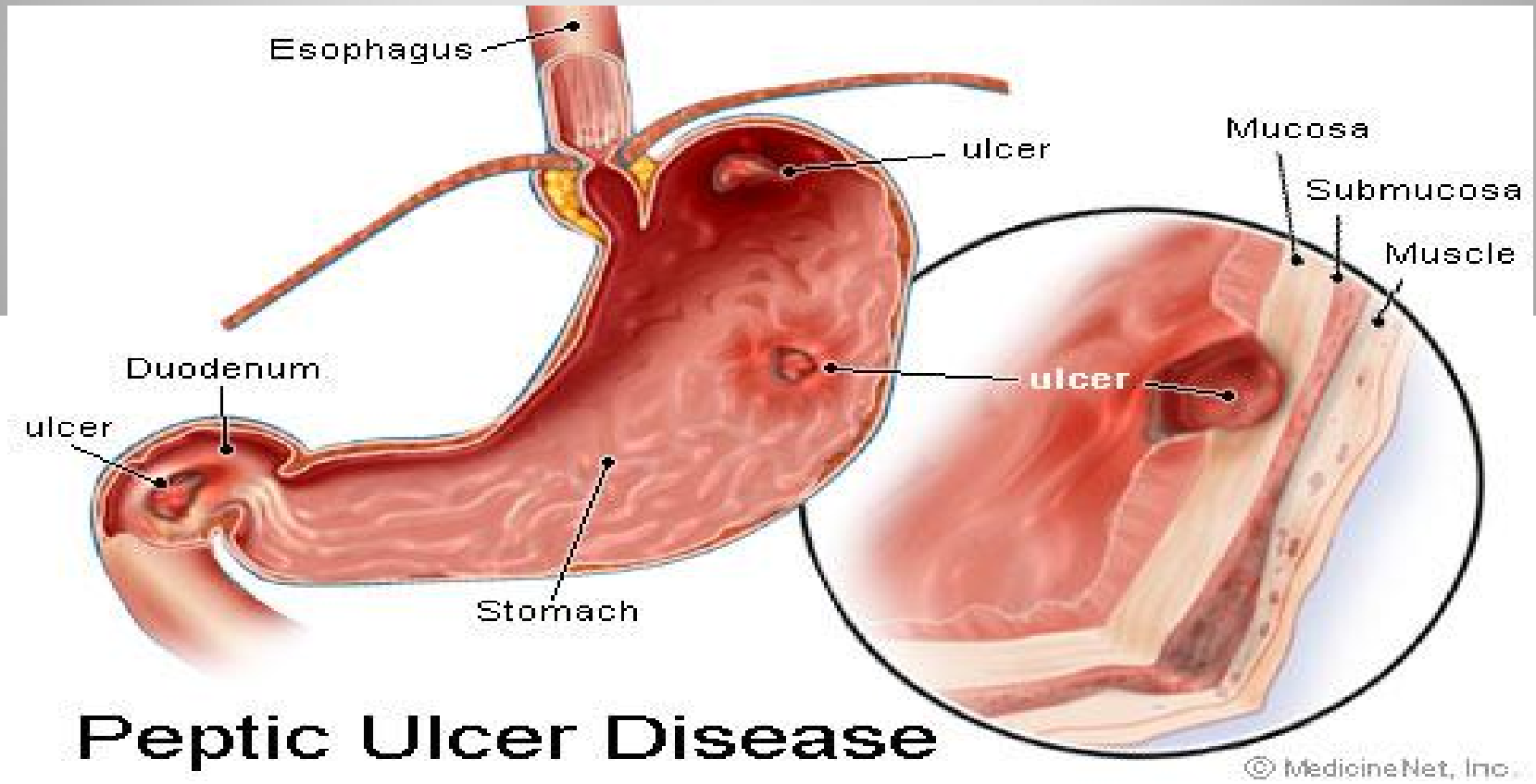
- Antacids are substances which reduce gastric acidity resulting in an increase in the pH of stomach & and duodenum. It is itself basic in nature. Weak bases are used for this purpose.

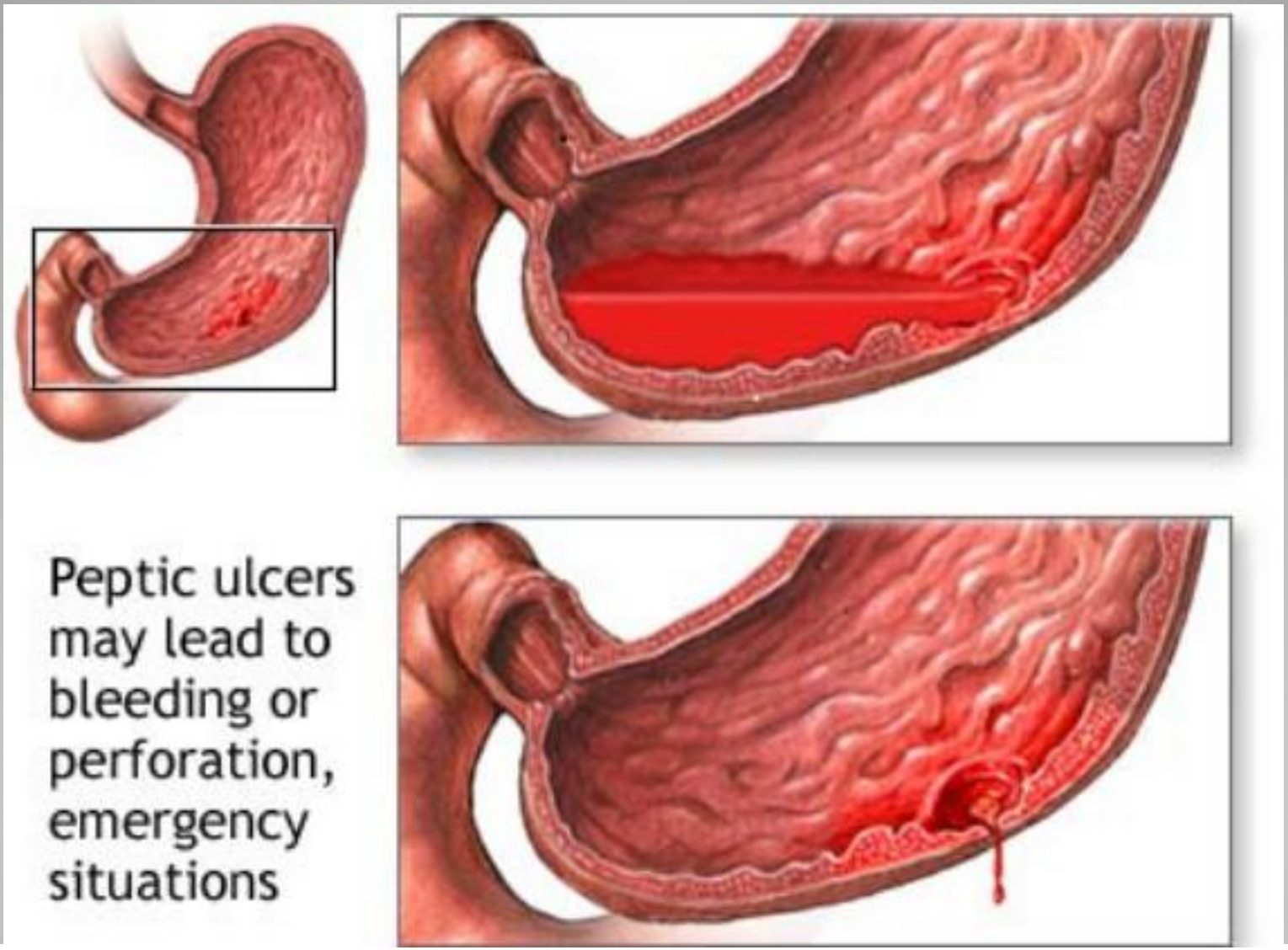
e.g. $Al(OH)_3$, $Mg(OH)_2$, $NaHCO_3$

- Stomach pH ranges from pH 1 when empty to pH 7 when food is present.
- The low acid pH is due to the presence of endogenous HCl that is always present under physiological conditions.
- When hyperacidity develops the results can range from *gastritis* (a general inflammation of the gastric mucosa) to *peptic ulcer* (erosion of the stomach lining).
- Peptic ulcer may be located

- Lower end of the esophagus (esophagul ulcer)
- Stomach (gastric ulcer)
- Duodenum (duodenal ulcer)

Diagram showing peptic ulcer didease




Peptic ulcers
may lead to
bleeding or
perforation,
emergency
situations

Antacid Therapy

Antacids are alkaline bases used to neutralize the excess gastric hydrochloric acid associated with gastritis and peptic ulcers.
This in turn inactivates pepsin (works best in low pH) which is a proteolytic enzyme that is thought to mediate tissue injury in ulcer disease.

Side-effects of antacid therapy:

- **Acid rebound** – If the gastric pH is raised too much, acid rebound may occur. The stomach may secrete additional HCl to lower the pH that might consume the antacid. The gastric contents including the antacid will be emptying into intestine and therfore the excess acid secreted into the stomach may lead to a hyperacidic condition, so worsening the ulcer.

Side-effects of antacid therapy (contd):

- **Systemic alkalosis :** If the antacid is sufficiently water-soluble and is composed of readily absorbable ions, the antacid may be absorbed and exert its alkaline effects on body's buffer systems. Example of such an antacid is sodium bicarbonate.
- **Sodium content** : Most available antacids are low in sodium so patients with sodium-restricted diets must be advised on this.
- **Local effects in the gastrointestinal tract** : Antacids containing calcium and aluminium salts, after being converted to soluble salts by gastric acid tend to be constipating and that containing magnesium salts tend to have a laxative effect.

Flow chart of Rebound acidity :

NaHCO3 + HCl → (pH) Alkaline media → Stimulation of oxyntic cells

Stimulation of oxyntic cells → Secretion of HCl to balance the acidity

Secretion of HCl to balance the acidity → Need excess NaHCO3

Need excess NaHCO3 → Reaction occurs & form alkaline media

Reaction occurs & form alkaline media → Then again rebound acidity

Then again rebound acidity → Stimulation of oxyntic cell occurs (Rebound acidity)

Stimulation of oxyntic cell occurs (Rebound acidity) → Secretion of HCl → Excess HCl

Excess HCl → Infection of stomach

Infection of stomach → Ulcer

Criteria of an ideal antacid:

An ideal antacid should have the following criteria :

1. The antacid should not be absorbable or cause systemic alkalosis.
2. The antacid should not be laxative or cause constipation.
3. The antacid should exert its effect rapidly and over a long period of time.
4. The antacid should buffer in the pH 4-6 range.
5. The reaction of the antacid with gastric hydrochloric acid should not cause a large evolution of gas.
6. The antacid should probably inhibit pepsin.

An ideal antacid should be

- **have a rapid onset**
- **provide a continuous buffering action**

Antacids with rapid onset – calcium carbonate, MgO, $Mg(OH)_2$

with intermediate onset – magnesium aldrate, magnesium carbonate

with slow onset – magnesium trisilicate, Al compounds

Dosing interval of antacid :

Duration of buffering action is largely determined by **when the antacid is administered**.

If administered while food is in the stomach, the buffering action will last for 2 hours.

An additional dose 1 hour after the meal will increase the buffering time by 1 hour.

Therefore **ideal dosing interval** is **between 1 and 3 hours after meals and at bedtime.**

Neutralizing capacity :

Antacids are compared quantitatively in terms of acid neutralizing capacity (ANC).

ANC may be defined as the number of milliequivalents of hydrochloric acid required to maintain 1 ml of antacid suspension at pH 3 for 2 hours *in vitro.*

ANC depends on crystal form, precipitants used, presence of reactive suspension agents of the antacids.

ANC and rate of neutralization of the different antacids differ from one another.
For e.g In 60 mins, 5ml of Aluminium hydroxide suspension will neutralize 6.5 mEQ of acid but 5ml of aluminium hydroxide and magnesium hydroxide will neutralize 42 mEQ of acid.

Classification of antacids

Classification :

There are two types of Antacids

- Systemic
- Non-systemic

Systemic antacids --->soluble and readily absorbed e.g NaHCO3

Nonsystemic antacids -----> insoluble and not readily absorbed and does not produce systemic effects e.g. $Al(OH)_3$, $Mg(OH)_2$

Systemic antacids :

- It is soluble & systemically absorbed.
- Capable of producing systemic alkalosis.
  e.g. $NaHCO_3$

  Sodium carbonate is highly water soluble & potent neutralizer, but it is not suitable for peptic ulcer because of risk of ulcer perforation due to production of carbon dioxide in stomach.
  It may lead to electrolyte disturbances, may lead to alkalosis, it may worsen edema and cause congestive heart failure because of sodium ion load (it causes sodium retention).

NaHCO3 +HCL--->NaCl+CO2+H2O

Preparation of systemic antacid

Method 1 for Preparation of $NaHCO_3$:

1. By passing strong brine containing high concentration of ammonia through a carbonated tower where it is saturated with carbon dioxide under pressure. The ammonia & carbon dioxide reacts to form ammonia bicarbonate which is allowed to react with NaCl to precipitate $NaHCO_3$ which is separated by filtration.

$NH_3 + H_2O + CO_2 \dashrightarrow NH_4HCO_3$

$NH_4HCO_3 + NaCl \dashrightarrow NaHCO_3$

Method 2 for Preparation of $NaHCO_3$:

2. it can also be prepared by covering sodium carbonate crystals with water and passing carbon dioxide to saturation.

$$Na_2CO_3 + H_2O + CO_2 \dashrightarrow NaHCO_3$$

Non-systemic antacids :

They are insoluble & poorly absorbed systemically.

e.g. $Al(OH)_3$, $Mg(OH)_2$, $CaCO_3$ etc.

- In case of $Mg(OH)_2$, it has low water solubility and has the power to absorb and inactive pepsin and to protect ulcer base.
- In case of $Al(OH)_3$, it is a weak and slow reacting antacid.
- In case of $CaCO_3$, it is a potent antacid with rapid acid neutralizing capacity, but in long term use it can cause hypercalciuria, hypercalcemia and formation of calcium stone in kidney.

Aluminium containing Antacids:

- Aluminium Hydroxide, $Al(OH)_3$
- Aluminium Phosphate, $AlPO_4$

Aluminium Hydroxide, $Al(OH)_3$

Aluminum Antacids are Nonsystemic and widely used and are ideal buffers in the pH 3-5 region.

Aluminum hydroxide is recognized in two forms in USP.

1. Gel USP XVIII: White viscous suspension, small amount of clear liquid may separate on standing.It has a pH 5.5-8.0. USP permits inclusion of flavoring and antimicrobial agent.

2. Dried Gel USP XVIII: White, odourless, colorless, tasteless, amorphous powder, insoluble in water and alcohol but soluble in dilute mineral acids.

Aluminium containing Antacids:

Forms:

- Aluminum Hydroxide Gel USP XVIII (suspension)
  - contain aromatics and sweetening
  - not more than 0.5% preservatives
- Dried Aluminum Hydroxide Gel USP XVIII (powder)
  - colloidial – great adsorptive powers
  - amphoteric characters

Ideal buffers in the pH 3-5 region due to their amphoteric character.

Acid neutralization by $Al(OH)_3$:

- $Al(OH)_3$ is considered as ideal antacid. It is soluble in acidic media. The overall mode of action of an Al-base antacid proceeds in a series of steps depending on the amount of antacid & the pH.

- Antacid reacts with water to form a complex.

$$Al(OH)_3 + 3H_2O \longrightarrow [Al(H_2O)_3.(OH)_3]^0$$

Complex (Base)

Acid neutralization by $Al(OH)_3$ cont....

The complex is soluble in acid media.

$[Al(H_2O)_3.(OH)_3]^0 + H_3O^+ \rightarrow [Al(H_2O)_4.(OH)_2]^+ + H_2O$

Base acid conjugated acid conjugated base

$[Al(H_2O)_4.(OH)_2]^+ + H_3O^+ \rightarrow [Al(H_2O)_5.(OH)]^{++} + H_2O$

$[Al(H_2O)_5.(OH)]^{++} + H_3O^+ \rightarrow [Al(H_2O)_6]^{+++} + H_2O$

Hexaquoaluminium ion

This H_3O^+ acid is present in the stomach.

Commercial Preparation of $Al(OH)_3$ gel :

Aluminium hydroxide gel is an aqueous suspension of hydrated aluminium oxide with different amounts of basic aluminium carbonate & bicarbonate. When a hot solution of K-alum is added slowly to a hot solution of Na_2CO_3, (at 70^0C), $Al(OH)_3$ is produced.

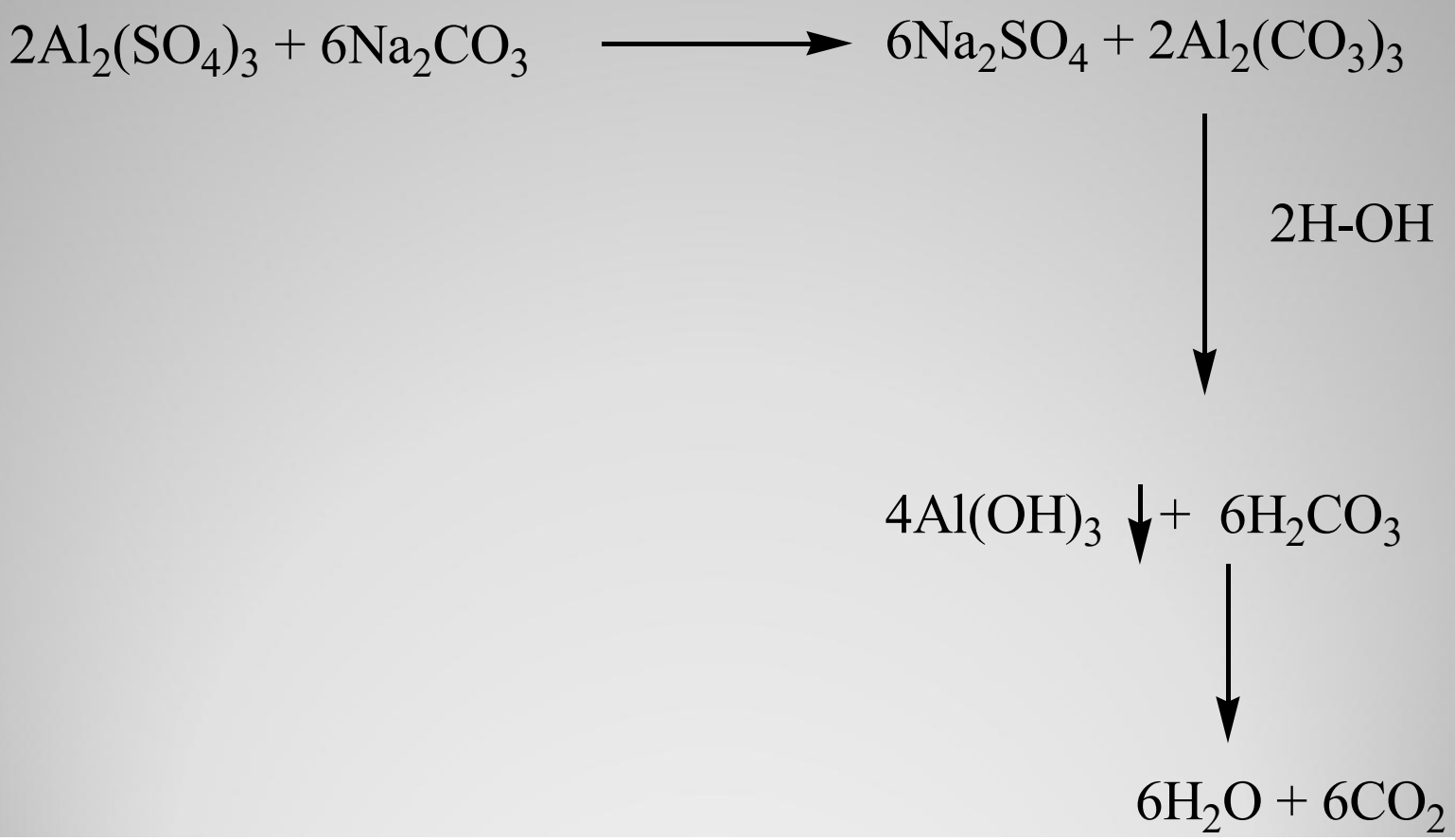
$$Na_2CO_3 + K_2SO_4.\ Al_2(SO_4)_3 + H_2O \dashrightarrow K_2SO_4 + Na_2SO_4 + Al(OH)_3 + CO_2$$

Method of Preparation :

It is prepared by dissolving sodium carbonate in hot water & the solution is filtered. To the filtrate add clear solution of alum (Aluminium salt, chloride or sulphate) in water with constant stirring.

Add more of water and remove all gas. The Aluminium Hydroxide precipitate out, collect the precipitate , wash and suspend in sufficient purified water.

Reaction occurred during preparation of $Al(OH)_3$ gel:



- **Purification :**
  The ppt $Al(OH)_3$ is washed thoroughly with hot water until it is free from SO_4^{-2} ion which is confirmed with the addition of some $BaCl_2$ to the filtrate.
  Filtrate + $BaCl_2$ --→ $BaSO_4$ (SO_4^{-2} present)
  --→ No change (SO_4^{-2} absent)

- **Adjustment of the gel :**
  The gel is adjusted with distilled water. $Al(OH)_3$ gel USP is a suspension containing the equivalent of not less than 3.6% & not more than 4.4% of Al_2O_3 per 100 g of $Al(OH)_3$.

- **Improvement of the formulation :**
  The following substances are added --
  1. Viscosity imparting agent : Glycerin
  2. Flavoring agent (0.01-0.05%): Peppermint oil
  3. Sweetening agent : Sucrose or saccharin
  4. Preservative (0.1 – 0.5%) : Sodium Benzoate

Advantages of $Al(OH)_3$:

1. Long duration of action.
2. Does not produce systemic alkalosis.
3. ANC is high.

Disadvantages of $Al(OH)_3$:

1. Slow onset of action.
2. Phosphorous depletion (forms insoluble $AlPO_4$ that results in increased phosphate excretion).
3. Osteomalacia (Softening of the bones due to a lack of vitamin D) & Osteoporosis (Thinning of bone tissue and loss of bone density over time).
4. Neurotoxicity in renal failure.
5. Can cause constipation.

Dose :

500 mg to 1800 mg 3 to 6 times a day between meals & bedtime

$Al(OH)_3$ is constipating.

Reason : The product of the reaction of aluminium hydroxide and HCl is the water soluble astringent salt aluminium chloride that causes constipation. It eventually forms the insoluble aluminium phosphate salt in the intestinal tract thus resulting in increased fecal phosphate excretion.

Constipation Mechanism of $Al(OH)_3$:

$$Al(OH)_3 + 3HCl \text{ -----}\rightarrow AlCl_3 + 3H_2O$$
Soluble

$$Al^{3+} + PO_4^{3-} \text{ -----}\rightarrow AlPO_4$$
Insoluble

$$Cl^- \text{ ----------}\rightarrow \text{Reabsorbed}$$

Pharmacological action of $Al(OH)_3$:

- It neutralizes the excess gastric acid and prevent the hyperacidity.
- After neutralization the available Al^{3+} conc. is raised which in turn gives rise to some astringent and antiseptic property.
- Pepsin & intestinal bacteria are adsorbed by Al(OH)3, gel and thus acts as a adsorbent in the prevention of ulcer creation.
- Due to its astringent and demulcent properties it forms a protective coating over the ulcer creator.
- It stimulates mucous secretion which enhances the mucosal barrier to acid.

Aluminium phosphate, $AlPO_4$

- used in place of aluminium hydroxide gel where loss of phosphate may be problem to the patient.
- Form : Aluminium Gel Phosphate N.F. XIII (Phosphogel)
- It is a white, viscous suspension from which small amounts of water may separate on standing.
- It has a pH between 6.0 and 7.2
- It has same adsorptive and astringent properties as $Al(OH)_3$.

Calcium containing antacids:

Forms :

CALCIUM CARBONATE

- Precipitated chalk
- Fast action
- Found in combinations with Mg antacids
- In Lozenges and Oral suspension

TRIBASIC CALCIUM PHOSPHATE

- Precipitated Calcium Phosphate, Tertiary Calcium Phosphate, Calcium Phospate
- Found in nature as **phosphrite** (phosphate rock) and **apatite**
- No gas produced (no flatulence)
- Does not alkalize the system

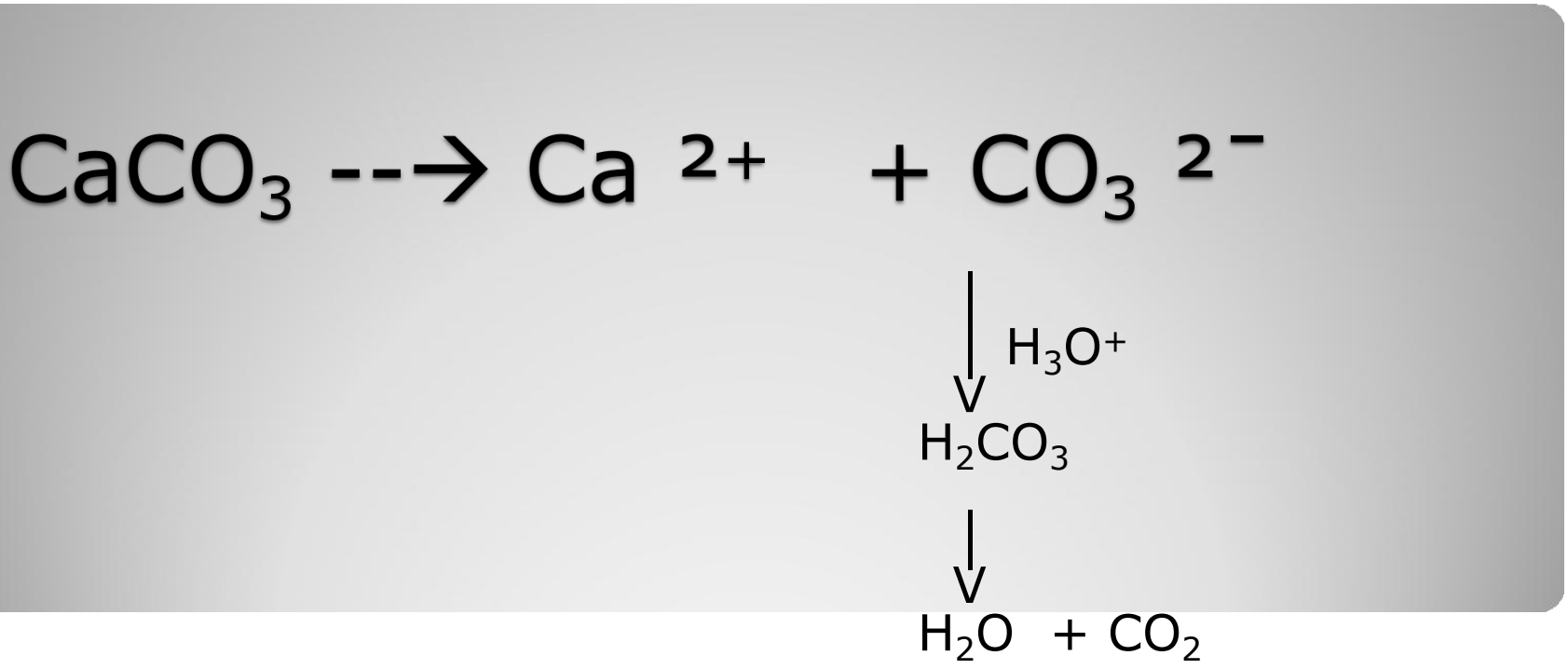
- Calcium containing antacids differ from aluminium antacids because their action depends on their basic properties and aluminium antacids' action depends on their amphoteric character.
- Ca^{++} are **rapid acting**
- Largely **nonsystemic**

Side-effects:

- Milk-alkali syndrome (Burnett syndrome) occurs during prolonged administration of large doses of sodium bicarbonate or calcium carbonate with large amounts of milk.
- This may cause acute alkalosis, renal insufficiency, hypercalcemia, hyperphosphatemia and azotemia.
- It causes constipation so used with Mg antacids.

Precipitated Calcium Carbonate USP XVIII

- It is a fine, white, odorless, tasteless microcrystalline powder which is stable in air.
- Practically insoluble in water but solubility is increased in presence of ammonium salt or carbon dioxide.
- Presence of any alkali hydroxide reduced its solubility.
- Insoluble in alcohol but dissolves with effervescence in diluted acetic, hydrochloric and nitric acis.
- Popular antacid due to its **fast action**.
- As gastric HCl consumes the solubilized calcium carbonate, more goes into solution. This process continues until the acid or calcium carbonate is consumed.



Usual dose : 1gm four to six times a day

Magnesium containing antacids:

Forms :

- **MAGNESIUM CARBONATE**
- Hydrated mixture of magnesium carbonate and magnesium hydroxide
- Dissolves as carbonate and hydroxide are consumed.
- **MAGNESIUM HYDROXIDE**
- Bulky, white powder
  Used as laxatives in high doses (salt action).
- **MILK OF MAGNESIA**
- Suspension of magnesium hydroxide with citric acid to minimize the interaction of glass and magnesium hydroxide
- Very popular antacid and laxative.
- **MAGNESIUM OXIDE**
- Magnesia.
- Light Magnesium Oxide hydrolyzes faster than heavy Magnesium oxide.

Magnesium containing antacids:

- There are a large number of official magnesium containing antacids.
- Except for magnesium trisilicate they all function in the same manner.
- They are poorly soluble salts which only go into solution as acid consumes the small amount of anion already in solution .
- As the pH of the stomach approaches neutrality the rate of dissolution of the magnesium salt slows down and stops at neutrality.
- So it is the anion rather than the magnesium cation that confers the antacid properties.
- The magnesium cation is responsible for these group of antacids to be laxative.
- For this reason they are found in combination with aluminium and calcium antacids to balance the constipative and laxative actions.

- **Preparation of $Mg(OH)_2$:**

They can be prepared by treating Mg salt with NaOH resulting $Mg(OH)_2$ precipitate & Na salts.

$$MgSO_4 + 2NaOH = Mg(OH)_2 \downarrow + Na_2So_4$$

$$MgCl_2 + 2NaOH = Mg(OH)_2 \downarrow + 2NaCl$$

- **Mechanism of action of $Mg(OH)_2$:**

  $Mg(OH)_2$ is very less soluble & only goes into solution when there is acid & already contain minute amount of anion present in the stomach. In presence of acid $Mg(OH)_2$ will dissolve the following way –

  $$Mg(OH)_2 \xrightarrow{\text{acid}} Mg(OH)_2$$

  (solid) (dissolved)

  Dissolved $Mg(OH)_2 \longrightarrow Mg(OH)^+ + (OH)^-$

  $$Mg(OH)^+ \longrightarrow Mg^{++} + (OH)^-$$

  Now, (OH)- is the determine factor which will participate with

- **Mechanism of action of $Mg(OH)_2$ cont.... :**

  proton from gastric HCl along with water & thus neutralizes the acid, leaving the counterpart Mg^{+2}

  $$HCl \dashrightarrow H^+ + Cl^-$$

  $$H_2O + H^+ \dashrightarrow H_3O^+$$

  $$(OH)^- + H_3O^+ \dashrightarrow 2H_2O$$

  Now Mg binds with Cl- to form insoluble MgCl2 which is mainly responsible for laxative actions.

  $$Mg^{++} + 2\ Cl^- \dashrightarrow MgCl_2$$

- **Laxative mechanism of $Mg(OH)_2$:**

The magnesium cation is responsible for the laxative action of magnesium containing antacids.

$$Mg(OH)_2 + 2HCl = MgCl_2 + 2H_2O$$

- **Advantages of $Mg(OH)_2$:**
  1. Fast onset of action.
  2. No systemic alkalosis.
  3. High ANC.
- **Disadvantages of $Mg(OH)_2$:**
  1. Short duration of actions.
  2. Laxative
  3. Hypermagnesia.
  4. Contraindicated in kidney patients.
- **Dose of $Mg(OH)_2$:**
  300 mg to 600 mg as antacid per day. 2 to 4 gm as cathartic per day.

Milk of Magnesia :

- Milk of Magnesia USP XVIII is a 7-8.5% w/w suspension of magnesium hydroxide, which may contain 0.1% citric and not more then 0.05% of a volatile oil or a blend of volatile oils, suitable for flavoring purpose.
- It is a white, opaque, more or less viscous suspension from varying proportion of water usually separate on standing and has a pH of about 10.
- Storage at temperature not exceeding 35◦C but not freezed.
- **Dose**: As antacid: 5 ml four times a day,
  As cathartic: 15 to 30 ml daily.

Why citric acid is added in the preparation of milk of magnesia ?

Milk of magnesia , USP is a suspension of magnesium hydroxide containing not less than 7% and not more than 8.5% of $Mg(OH)_2$

For purposes of minimizing the alkalinity of milk of magnesia 0.1% citric acid is added.

Normally, $Mg(OH)_2$ ionizes into Mg^{2+} & OH^- ion. The citric acid ($C_6H_5O_7$) upon addition reacts immediately to form magnesium citrate which ionizes to supply magnesium ion & citrate ion.

$$Mg(OH)_2 \longrightarrow Mg^{2+} + 2\ OH^- \text{ ---------(i)}$$

$$Mg_3(C_6H_5O_7) \longrightarrow 3Mg^{2+} + 2C_6H_5O_7^{3-} \text{ ---------(ii)}$$

This increases the concentration of Mg^{2+} ions

As the aqueous suspension stands in contact with the glass container , additional hydroxide is formed from the hydrolysis of the sodium silicate of the glass.

$Na_4SiO_4 + 3H_2O \longrightarrow H_3SiO_4 + 4Na^+ + 3OH^-$

As the pH increases, the law of mass action requires the reaction (i) be reversed and magnesium hydroxide reformed as the excess hydroxide from the glass is consumed.

Due to the presence of citric acid there are enough magnesium cations available to react with excess hydroxide from the glass container .

The end result is a product with a milder, less chalky taste. The alkalinity contributed by the glass container is like wise counteracted.

Antacid combinations:

Because no single antacid meets all the criteria for an ideal antacid, several products are on the market containing mixtures of antacids.

Every single compound among antacid have some side effect especially when used for longer period or used in elderly patients. To avoid certain side effects associated with antacids, combinations of antacids are used such as :

(i) Magnesium and aluminium containing preparation e.g. magnesium hydroxide a fast acting antacid with aluminium hydroxide which is a slow acting antacid.

(ii) Magnesium and calcium containing preparation where one is laxative and the later one is constipative in nature

Advantages of antacid combinations:

Different advantages are given below –

1. To balance laxative & constipation action :

When laxatives & constipating compound are formulated in a mixture, the gastro-intestinal disturbances may not occur or occur less.

$Al(OH)_3$ + $Mg(OH)_2$ ⟶ less or no GI disturbances

250 mg (Constipating agent) + 400 mg (Laxative)

2. To maintain fastation & solvation :

To increase total buffering time, a fast acting compound with slow acting antacid are formulated in mixtures.

$NaHCO_3$ + $Mg(OH)_2$ or $MgCO_3$ ⟶ Maintain fastation and solvation

Advantages of antacid combinations (contd)

3. To reduce toxicity :

In a single entity antacids may cause high toxicity. So to reduce toxicity antacids are formulated in a mixture.

4.To increase patient tolerance :

Mixture of antacids increase the patient tolerance rather than by multiple separate preparation.

5. For bone formation :

Long time continuous use of Al^{+++} may produce lack of PO_4^{3-} which inhibit the bone formation.

$$Al(OH)_3 + HCl \longrightarrow AlCl_3 + H_2O$$

$$AlCl_3 \longrightarrow Al^{3+} + 3Cl^-$$

$$Al^{3+} + PO_4^{3-} \longrightarrow AlPO_4$$

Examples of antacid combinations:

Aluminium Hydroxide Gel- Magnesium Hydroxide combinations

- USP recognizes two dosage forms : a **suspension and a tablet.**
- In either dosage form either aluminium hydroxide gel or magnesium hydroxide may predominate.
- **Alumina and Magnesium Oral suspension U.S.P XVIII** contains the equivalent of 4% aluminium oxide (Al_2O_3) and 2% magnesium hydroxide $Mg(OH)_2$. Dose : 15ml four to six times a day.
- **Magnesia and Aluminium Oral Suspension U.S.P XVIII** contains the equivalent of 2.2% aluminium oxide and 3.8% of magnesium hydroxide. Dose: 1 to 2 tablets four to six times a day.
- Same for the two tablet forms.

Examples of antacid combinations:

Magaldrate N.F. XIII

- It is a chemical combination of aluminium hydroxide and magnesium hydroxide.
- It contains the equivalent of 28 to 39% magnesium oxide and 17 to 25% of aluminium oxide.
- It occurs as a white, odorless, crystalline powder which is insoluble in water and alcohol but soluble in dilute solutions of mineral acids.
- Usual dose: 400 to 800 mg as required preferably taken between meals and at bedtime.

Examples of antacid combinations:

Calcium Carbonate – containing Antacid Mixtures

- can be found in combination with aluminium hydroxide gel to yield products that have a rapid onset with prolonged action.
- Can also be found with magnesium-containing antacids to balance the constipative effect of calcium with the laxative effects of magnesium.

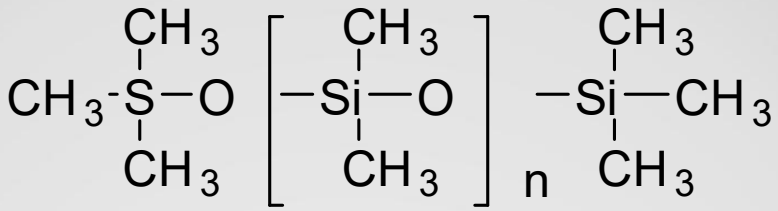
Simethicone containing antacids

Defoaming agent simethicone has been added to some antacids to decrease flatulence problem.

Antacids & Antiflatulents

- **Simethicone**

- **Simethicon is a mixture of full methylated linear siloxane polymers containing repeating units of the formula [-$(CH3)_2$ SiO_2]n, stabilized with trimethylsiloxy end- bulking units of the formula [$(CH3)_3$ SiO-] and silicon dioxide.**
- **Translucent, gray, viscous fluid, Sp. gravity 0.064 – 0.984, viscosity not less then 300 centistokes at 25◦C.**



- **<u>Use:</u> Antiflatulent, gastric protective to deform gastric juice in order to decrease the tendency to gastro esophageal reflux.**
- **<u>Dose:</u> 40-80 mg (tablet) 4 times a day after each meal & at bedtime.**

Protectives and Adsorbents :

This group of gastrointestinal agents are used commonly used for the treatment of mild diarrhea.

Criteria :

- Treatment for mild diarrhea
- Contain antibacterial agent
- Decreases peristalsis
- Adsorbent-protective – adsorb toxins, bacteria, and viruses.

Diarrhea :

- Diarrhea results when some factor impairs digestion and /or absorption, thereby increasing the bulk of the intestinal tract.
- This increased bulk stimulates persitalsis, propelling the intestinal contents to the anus.

Causes of Diarrhea :

- Diet
- Gastro-intestinal infections
- Certain damage
- Psychological factors
- Inflammation or irritation of the mucosa of the intestines

Classification :

Diarrhea may be of several types :

- Acute Diarrhea- Caused by bacterial toxins, chemical poisons, drugs, allergy, disease. These agents for causing acute diarrhea causes effects ranging from tissue damage to irritation to flow of electrolytes from body fluids into the intestinal tract, there by increasing the osmotic load of the intestinal tract.

- Chronic Diarrhea -Result from gastrointestinal surgery, carcinomas, chronic inflammatory conditions and other adsorptive defects.

- Loss of fluids and electrolytes can quickly lead to dehydration and electrolyte imbalance.

Treatment of diarrhea:

Most products for the treatment of diarrhea will consist of

- **Adsorbent properties** : These agents supposedly adsorb toxins, bacteria & viruses along with providing a protective coating of the intestinal mucosa. For example – Bismuth salt, Special clays & activated charcoal etc.
- **Antispasmodic** : These agents act directly on the smooth muscles of the gut to produce a spasm-like effect which decrease peristalsis & increases segmentation.
- **Antimicrobial agent** : It is only effective if there is an actual infection in the intestinal tract or during epidemic previously shown to be caused by a micro-organism.

Examples of protectives and adsorbents

1. Bismuth-Containing Products :

- They are used as antidiarrheals.
- They have a mild astringent and antiseptic action.

Bismuth Subnitrite N.F XIII

- occurs as a white, slightly hygroscopic powder
- gives an acid reaction using blue litmus paper
- practically insoluble in water and alcohol but readily dissolved by hydrochloric or nitric acid.
- can apparently inhibit pepsin

Milk of Bismuth N.F XIII

- It contains bismuth hydroxide and bismuth subcarbonate in suspension in water.
- It is made by converting bismuth subnitrite to bismuth nitrite by the addition of nitric acid.
- Then by treatment with ammonium carbonate and ammonia solution, bismuth nitrite is converted to bismuth hydroxide and subcarbonate. Usual dose : 5 ml

Reactions from pg 290 Book : Block and Roche

It is classified by N.F as an astringent and antacid

Bismuth Subcarbonate USP XVIII

- White or pale yellowish white odorless, tasteless powder
- topical protectant

2. Activated Clays and other Adsorbents :
This group is composed mainly of clays and have excellent adsorbent properties.

Kaolin N.F. XIII

- It is a native hydrated aluminium silicate, powdered and freezed from gritty particles.
- occurs as a soft, white, or yellowish white powder or as lumps.
- has an earthy or clay like taste and assumes a dark color when moistened with water.
- Insoluble in water, in cold dilute acids and in solutions of alkali hydroxides.
- found together with vegetable carbohydrate pectin
- Used as an adsorbent

Activated Charcoal USP XVIII – used as an adsorbent in the treatment of diarrhea and antidote for treatment of poisoning.

3. Magnesium Trisilicate

- **Magnesium Trisilicate** :
  It is a compound of MgO and SiO_2 containing varying proportion of water. Due to method of manufacture, it is more likely to be a mixture of magnesium metasilicate ($MgSiO_3$) and colloidal SiO_2, with varying amount of water.

- **Mechanism of Magnesium Trisilicate :**
  It has protective, neutralizing & laxative activity.

$$MgSi_3O_8 + 4HCl = 2MgCl_2 + \underbrace{H_4Si_3O_8}_{\underbrace{2H_2SiO_3 + SiO_2 + nH_2O}_{\text{collidal mixture}}}$$

The colloidal mixture containing silicon dioxide and silicic acid can protect the peptic ulcer from further acid and peptic attack and can adsorb pepsin.

- **Advantage:** 1. Protective action of ulcer
- **Disadvantage**: Siliceous nephrolith, Diarrhea.
- **Does**: usually 1-16 gm daily (4 times)
- **Use**: As antacid, as adsorbent/ protective.

Saline Cathartics

- Saline cathartics (purgatives) are agents that quicken and increase evacuation from the bowels.
- Laxatives are mild cathartics.

Cathartics are used for

1. To ease defecation in patients with painful hemorrhoids or other rectal disorders
2. To avoid excessive straining and concurrent increases in abdominal pressure in patients with hernias
3. To avoid potentially hazardous rises in blood pressure during defecation in patients with hypertension, cerebral, coronary and arterial diseases
4. To relieve acute constipation
5. To remove solid material from the intestinal tract before roentgenographic studies

Constipation

- Constipation is the infrequent or difficult evacuation of the feces.
- Causes of constipation:
  - Person resisting the natural urge to defecate that causes the fecal material to lose fluid and become hard
  - intestinal atony (lack of muscle tension) and intestinal spasm
  - emotions
  - drugs
  - diet

Remedy / Treatment:

- Foods with adds fibre/ roughage to the diet like fruits, vegetables and drinking lots of water
- saline cathartics and laxatives

How saline cathartics act?

- Saline cathartics act by increasing osmotic load of the GIT.
- They are salts of the poorly absorbable anions and sometimes cations.
- The body relieves the hypertonicity of the gut by secreting additional fluids into the intestinal tract.
- The resulting increased bulk stimulates peristalsis.

They are salts of poorly absorbable anions –H_2PO_4- (biphosphate), -$HPO4_2$- (phosphate), sulphates, tartarates, and soluble magnesium salt (cation).

Use of saline cathartics :

1. Saline cathartics are water soluble and are taken with large quantities of water. This prevents excessive loss of water from body fluids and reduces nausea vomiting if a too hypertonic solution should reach the stomach. They act in the intestine and a full cathartic dose produces a water evacuation within 3-6 hrs.

2. They are used for bowel evacuation before radiological, endoscopic and surgical procedures and also to expel parasite and toxic materials.

Side effects :

Small amounts of these drugs may be absorbed in the blood causing occasional toxicity. The absorption of magnesium may cause marked CNS depression while that of sodium worsens the existing congestive cardiac failure (CCF).

Examples of official saline cathartics

- Sodium Biphosphate N.F. XIII – colorless or white crystalline powder.
- Sodium Phosphate N.F XIII- white granular salt

Dose : 4 to 8 mg.

- Dried sodium Phosphate N.F – anhydrous white powder

Dose : 2 to 4 gm

- Effervescent Sodium Phosphate N.F. XIII – mixture of sodium bicarbonate, tartaric acid and citric acid.
- Potassium Sodium Tartarate N.F. XIII

Nonofficial saline cathartic : Sodium sulfate N.F XII,
Potassium phosphate N.F XII
Calomel N.F. XII

Calomel N.F. XII (Hg_2Cl_2) :

- Mercury chloride
- It has a thorough cleansing action, starting in the upper part of the small intestine.
- It has antiseptic property.
- Its action is based on its disproportionation in the alkaline small intestine forming free mercury and mercuric cation.
- Since mercuric cation is a strong intestinal irritant, the dose of calomel should be given in several portions spaced at 20 – 30 minute interval so that the irritant effect spreads over a longer portion of the intestine.
- Due to mercury poisoning it is advisable to follow the administration of calomel by saline cathartic within six hours.

Laxatives

There are 4 types of laxatives:

1. **Stimulant**
2. **Bulk-forming**
3. **Emollient**
4. **Saline**

Stimulant – The stimulant laxatives act by local irritation on the intestinal tract which increases peristaltic activity. Examples include : phenolphthalein, cascara extract, rhubarb extract, senna extract.

Bulk-forming – The Bulk-forming laxatives are made from cellulose and other nondigestible polysaccharides. They swell when wet, with the increased bulk stimulating peristalsis. Examples include: methyl cellulose, sodium carboxymethyl cellulose.

Emollient : The emollient laxatives act either as lubricants facilitating the passage of compacted fecal material or as stool softeners. Examples include mineral oil, d-octyl sodium sulfosuccinate, an anionic surface active agent.

Saline cathartics act by increasing the osmotic load of the GIT. They are salts of poorly absorbable anions $-H_2PO_4$- (biphosphate), -$HPO4_2$- (phosphate), sulphates, tartarates, and soluble magnesium salt.