

Lecture 1

Drugs used in Gastrointestinal tract

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Objectives

- To Familiarize students with the basic chemistry, pharmacokinetics, and pharmacodynamic principles and untoward actions of drugs which are used in the treatment of gastrointestinal disorders
- The discussion will be aimed at helping the student to develop a good understanding of the basic concepts which will be useful in the intelligent clinical application of the drugs.



Peptic ulcer syndrome

- **Definition: peptic ulcer:**

A condition in which there is a sharply circumscribed loss of tissue in the intestinal tract

- **Sites:**

- a. Stomach
- b. Duodenum
- c. Esophagus



Factors involved in the development of peptic ulcer

A. Digestive action of the acid in gastric juice .

Note: mucous membrane of the stomach is the only body tissue resistant to acids.

B. Contributing factors

- Excessive adrenal cortical activity
- Vascular congestion
- Emotional stress and tension
- Burns
- Disease and brain surgery
- Drugs



Drugs that can precipitate or aggravate peptic ulcer disease

- Alcohol
- Salicylate (Aspirin)
- Phenylbutazone
- Indomethacin
- Oxyphenbutazone
- Sulfinpyrazone
- Adrenal corticosteroids
- Corticotropin (ACTH)
- Niacin
- Reserpine
- Levodopa
- Potassium chloride



Pathophysiology of peptic ulcer

- Gastric mucosa is the only body tissue that is resistant to HCl acid, the mucosa has been attacked by digestive juices to such an extent as to expose the subjacent connective tissue layer (submucosa). This self-digestion occurs when the equilibrium between the corrosive hydrochloric acid and acid-neutralizing mucus, which forms a protective cover on the mucosal surface, is shifted in favor of hydrochloric acid. Mucosal damage can be promoted by *Helicobacter pylori* bacteria that colonize the gastric mucus.

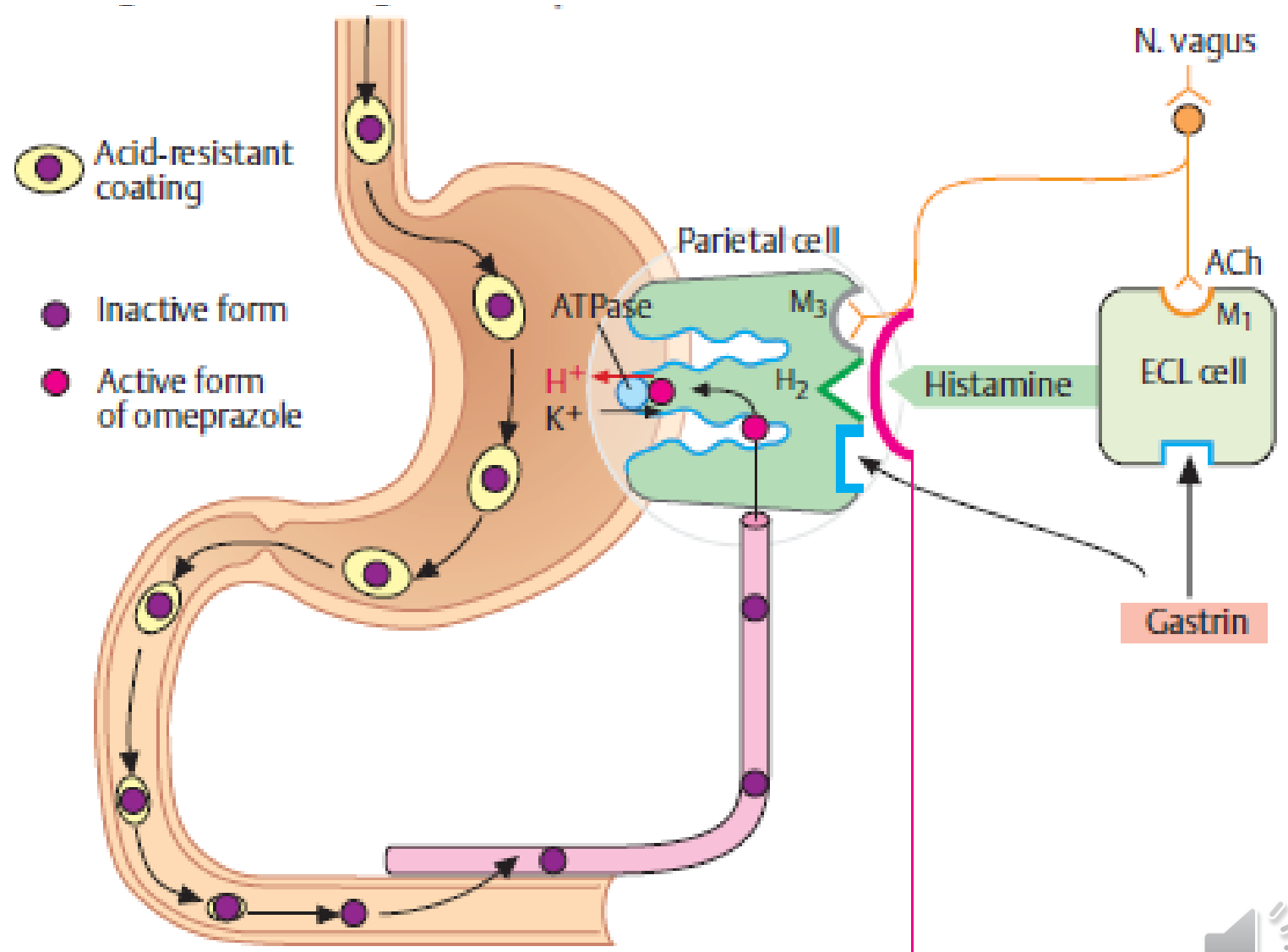


I. Acid secretion is stimulated by the following factors:

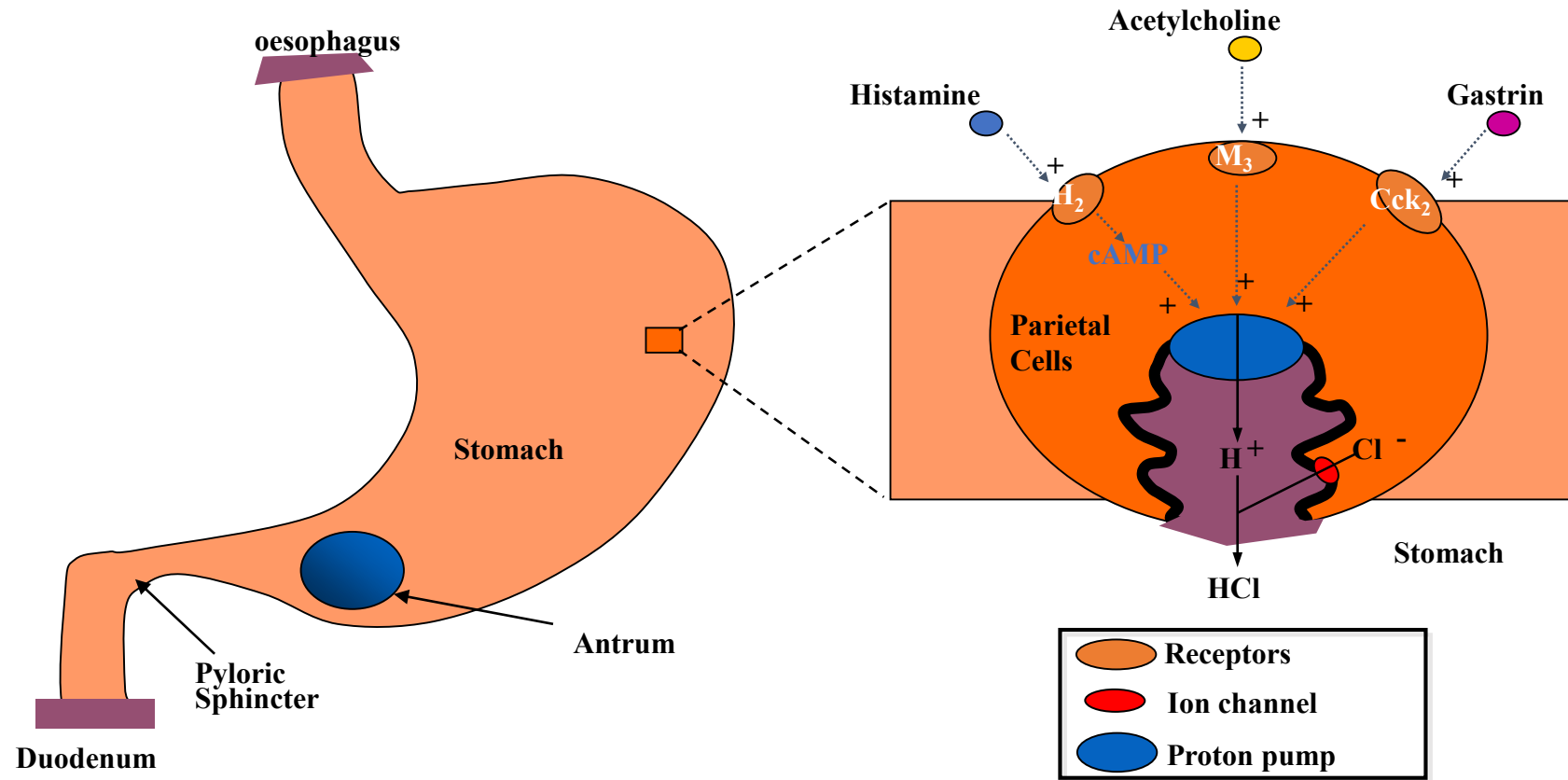
1. Gastrin hormone which is stimulated by food and pepsin
2. Acetyl choline
3. Histamine

II. Acid secretion is inhibited by:

1. Somatostatin (secretion of somatostatin is stimulated by HCl and it has a negative feed back inhibition on gastrin)
2. Prostaglandin E2



Parietal cells and gastric acid release



- Release of gastric acid is promoted by acetylcholine, gastrin and histamine
- *Physiological control of HCl secretion by fundic cells*
- *Histamine stimulates secondary messenger which stimulates cAMP that stimulates protein kinase and proton pump*



Symptoms and complications

1. Pain = outstanding symptoms

• Characteristics :

- Chronic in nature
- Periodic in occurrence
- Invariably gnawing pain (burning ache or pain in digestion in the upper abdomen that may become either worse or better with eating)
- Aching
- Burning in character
- Rhythmic in its relation to digestion cycle

2. Nausea : not common

3. Emesis : not common

4. Constipation : Frequent

5. No disturbance in appetite and patient may be overweight

6. No weight loss



Complications

- 1. Bleeding
- 2. Perforation

Investigations:

- X-rays
- Gastroscopy
- Acid content of the stomach



Therapeutic approaches are:

- (a) to reduce aggressive forces by lowering gastric acidity by neutralizing or decreasing proton output and slowing gastric emptying
- (b) to increase protective forces by means of mucoprotectants;
- (c) to eradicate *Helicobacter pylori* = (Antibiotics)
- (d) to support psychotherapy (sedatives and tranquilizers)
- (e) slowing gastric motility (emptying) : anticholinergics
- (f) Treatment of complications such as bleeding (by blood transfusion) and perforation (by surgery).

- Drugs are employed with the following therapeutic aims:
- (1) to relieve pain
- (2) to accelerate healing;
- (3) to prevent ulcer recurrence. .

Drugs for Gastric and Duodenal Ulcers

- **Antibiotic medications to kill H. pylori.**
 - Amoxicillin.
 - Clarithromycin.
 - Metronidazole.
 - Tinidazole.
 - Tetracycline.
 - and Levofloxacin.
- **Medications that block acid production and promote healing.**
 - Proton pump inhibitors (also called PPIs)
 - Omeprazole
 - Lansoprazole
 - rabeprazole
 - Esomeprazole
 - and Pantoprazole.
- **Acid blockers — also called histamine (H-2) blockers**
 - Ranitidine,
 - Famotidine,
 - Cimetidine
 - and Nizatidine.
- **Antacids that neutralize stomach acid.**
- **Medications that protect the lining of your stomach**
 - Sucralfate (Carafate)
 - and Misoprostol (Cytotec).



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- (2) to accelerate healing;
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Drugs for Lowering Acid Concentration

- **a. Acid neutralization (Antacids)**
- **b. Inhibitors of acid production**



Drugs for Lowering Acid Concentration

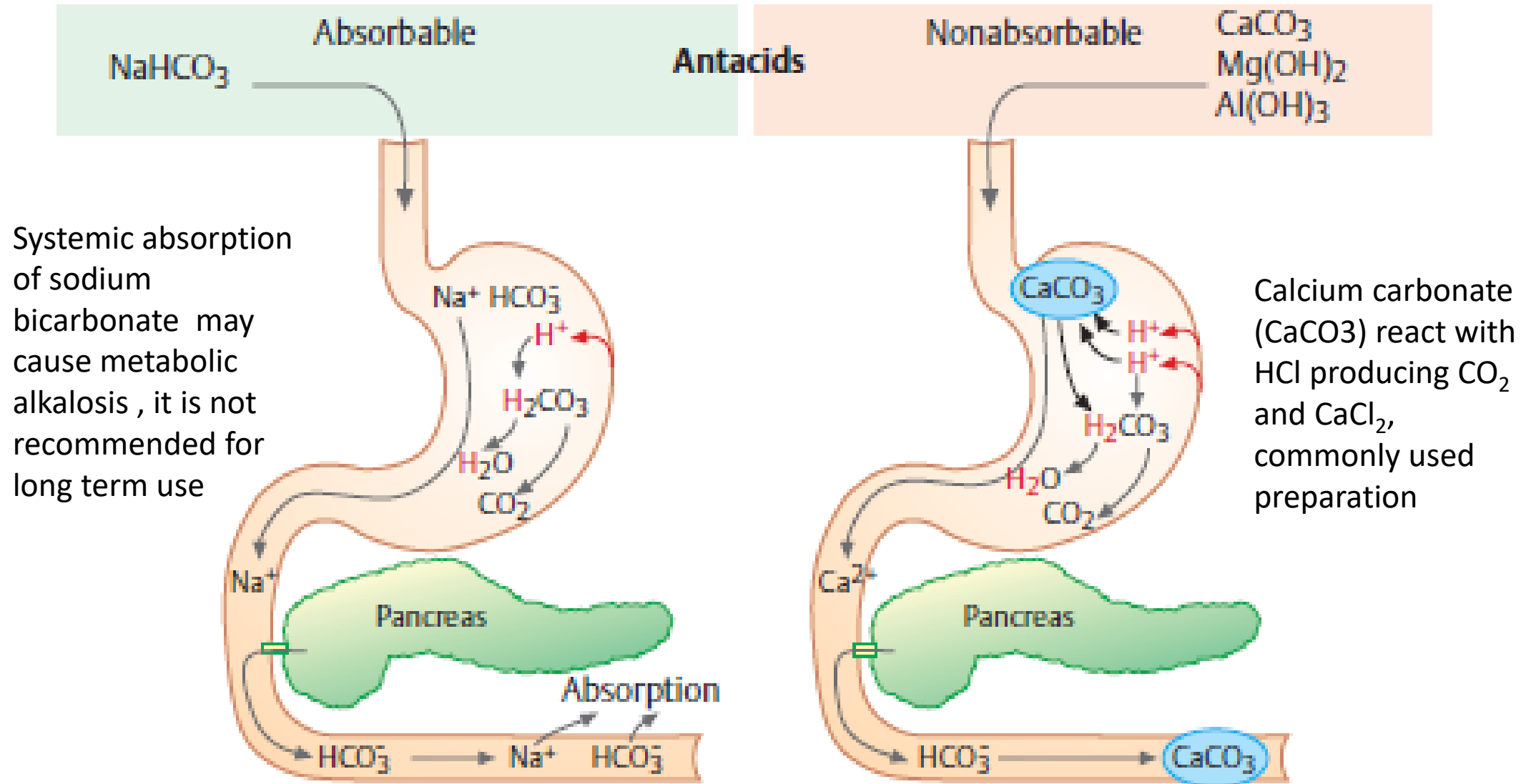
- Products vary widely in their chemical composition (mainly NaHCO_3 , CaCO_3 , $\text{Al}(\text{OH})_3$, $\text{Mg}(\text{OH})_2$, etc.
- **Antacids are**
 - a. Weak bases that react with gastric acids to form water (H_2O) and salts
→ this lowers the gastric acidity
 - b. Moreover pepsin is inactive at pH greater than 4 → the acid neutralization decreases the pepsin activity
- **The acid –neutralizing capacity depends on:**
 - a. The antacid capacity to neutralize HCl .
 - b. Stomach food intake , food delay , stomach emptying allowing more time for antacid reaction.



Drugs for Lowering Acid Concentration

- **Acid neutralization.**
- Proton binding groups such as CO_3^{-2} , HCO_3^{-} or OH^- , together with their counter ions, are contained in antacid drugs. Neutralization reactions occurring after intake of CaCO_3 and NaHCO_3 , respectively,
- With nonabsorbable antacids, the counter ion is dissolved in the acidic gastric juice in the process of neutralization. Upon mixture with the alkaline pancreatic secretion in the duodenum, it is largely precipitated again by basic groups, e.g., as CaCO_3 or AlPO_4 , and excreted in feces

Acid used to neutralize gastric acid



Side effects of acid neutralizing agents

- I. Aluminum hydroxide ($\text{Al}(\text{OH})_3$) causes constipation
- II. Magnesium hydroxide ($\text{Mg}(\text{OH})_2$) causes diarrhea (osmotic effect)
- III. In patients with normal renal function the absorption of cations from antacid e.g Mg^{+2} , Al^{+3} , and Ca^{+2} is usually not a problem, However in the presence of renal insufficiency, absorption of even small amounts may cause an increase in plasma levels of counter ions (e. g., magnesium intoxication with paralysis and cardiac disturbances).
- IV. Aluminum containing antacids can lead to hypophosphatemia and drug –drug interactions , e.g. Tetracyclines , Precipitation in the gut lumen is responsible for other side effects, such as reduced absorption of other drugs due to their adsorption to the surface of precipitated antacid; or phosphate depletion of the body with excessive intake of $\text{Al}(\text{OH})_3$.



1. Side effects of acid neutralizing agents

V. Antacid containing sodium salt can cause the following problems

- A. Na^+ ions remain in solution even in the presence of HCO_3^- rich pancreatic secretions and are subject to absorption, like HCO_3^-
- B. Because of the uptake of Na^+ , use of NaHCO_3 must be avoided in conditions requiring restriction of NaCl intake, such as hypertension, cardiac failure, and edema.

VI. Excessive intake of calcium carbonate along with calcium food e.g milk and milk products can cause hypercalcemia

N.B :Since food has a buffering effect, antacids are taken between meals (e. g., 1 and 3 hours after meals and at bedtime).

Non-absorbable antacids.

- Non-absorbable antacids are preferred.
- Non-absorbable antacids are used alone or in combination
- Because $\text{Mg}(\text{OH})_2$ produces a laxative effect (cause: osmotic action, and release of cholecystokinin by Mg^{2+} , or both)
- $\text{Al}(\text{OH})_3$ produces constipation (cause: astringent action of Al^{3+} ,
- These two antacids are frequently used in combination (e. g., milk of magnesia and magaldrate).



Combination $\text{Mg}(\text{OH})_2$ and $\text{Al}(\text{OH})_3$

- Therapeutics uses
- The laxative effect of $\text{Mg}(\text{OH})_2$ is deleted by the constipation effect of $\text{Al}(\text{OH})_3$. They produce the following:
 - a. Neutralization of HCl
 - b. Symptomatic relief of pain
 - c. They may promote healing of duodenal ulcers
- N.B: last line therapy
- N.B: Calcium carbonate may be used as supplements for treatment of osteoporosis

