

PHARMACOLOGY

Drugs Acting on Gastrointestinal System

Dr. R. K. Goel
Head
Dept. of Pharmacology
Institute of Medical Sciences
Banaras Hindu University
Varanasi – 5

Dr. G. Bhawani
Institute of Medical Sciences
Banaras Hindu University
Varanasi - 5

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Key words

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Digestants

These drugs are used to promote digestion of food as a replacement therapy in condition of their deficiency specially in atrophic gastritis, gastric carcinoma, pernicious anaemia or pancreatic insufficiency etc. Various proteolytic (pepsin, papain), lipolytic (lipases) and amylolytic (diastase and takadiastase) enzymes are used in combination as appetite stimulants and health tonics. Dilute hydrochloric acid (HCl) is advocated in severe achlorhydria. These are beneficial only when deficiency of these is marked, otherwise their routine use is irrational and unwarranted.

Digestants in Gastric Dysfunction

1. Hydrochloric acid- 5 to 10 ml of 10% HCl, diluted further in 100-200 ml of water may be sipped with a straw (to avoid direct contact with teeth) during meals. When taken in sufficient quantity HCl will help in enhancing the activity of pepsin (both of endogenous/exogenous source) and may prevent bacterial growth in stomach during achlorhydria.
2. Pepsin- it may be used with HCl in condition of deficiency. Dose- 20 to 100 mg/day in divided doses contained in various marketed enzyme preparations.
3. Papain- raw papaya contains papain which has got proteolytic activity. Dose-30-60 mg/day as advocated in different enzyme preparations.

Digestants in Pancreatic Insufficiency

1. Diastase/takadiastase- They are amylolytic enzymes obtained from fungus *Aspergillus oryzae*.
Dose- Takadiastase-150-160 mg/day and diastase-around 20 mg/day in various marketed preparations.
2. Pancreatin- it is a mixture of various pancreatic enzymes like amylase, trypsin and lipase, generally obtained from hog/pig pancreas. It reduces fecal fat and nitrogen content. It should be given by enteric coated capsule to prevent its own digestion in stomach by pepsin. It can produce adverse reactions like nausea, diarrhea and uric acid renal stones.

Dose-150-250 mg/day in various marketed preparations with simethicone (25 mg) or tauroglycocholate (50 mg).

Emetics and Antiemetics Drugs

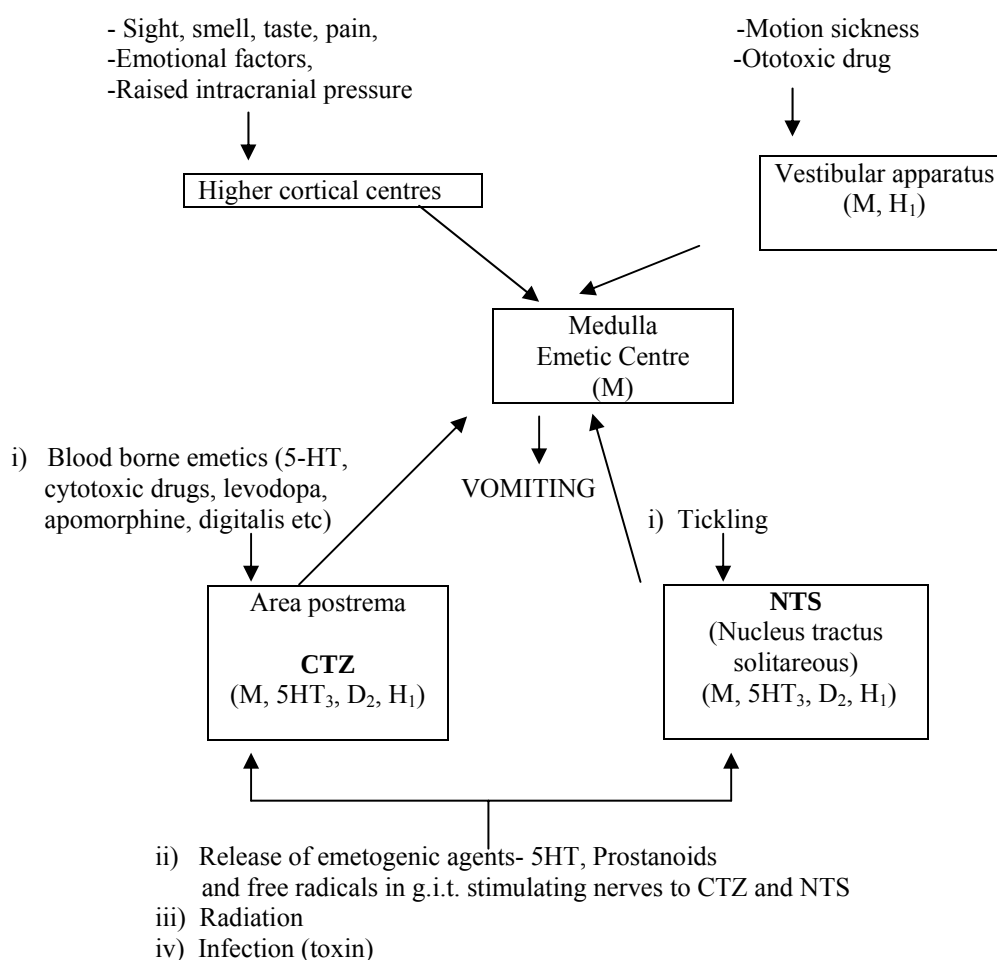
Vomiting or emesis is a protective mechanism which leads to expulsion of harmful substances from the upper gastrointestinal tract (GIT). It involves the active participation of vomiting centre (VC) present in the medulla oblongata either through direct afferent input to it or via chemoreceptor trigger zone (CTZ) and nucleus tractus solitarius (NTS) present in area postrema. Impulses from the higher cortical centres due to unpleasant sight, smell or thought, pain, emotional factors and increase in intracranial pressure etc. may induce vomiting. Similarly impulses via cerebellum arising from vestibular apparatus (inner ear) stimulation either by frequent change in body motion or its stimulation by ototoxic drugs like aminoglycosides can also induce vomiting.

Both NTS and CTZ act as relay station for VC and receive impulses from GIT, heart, testis, throat, and other viscera through vagus and sympathetic nerves. Afferents from fauces run through NTS to the VC. CTZ which lies outside the blood brain barrier is accessible to circulating drugs (cytotoxic drugs, levodopa, apomorphine, digitalis, ergot alkaloids etc.), mediators (5-Hydroxytryptamine released by platelets or inflamed site), toxins (infection),

hormones (oestrogen etc.), radiation etc. The motor pathways activated by VC lead to relaxation of cardiac end of stomach and contraction of diaphragm and abdominal muscles to increase the intragastric pressure allowing the gastric contents to expel out. Vomiting generally follows the inhibition of gastric motility believed to be mediated through dopamine receptor (DA₂).

VC contains mainly cholinergic muscarinic (M) receptors, whereas vestibular apparatus has both M and histamine-1 (H₁) receptors. CTZ and NTS have variety of receptors like M, H₁, DA₂ and 5-hydroxytryptamine-3 (5-HT₃). Enkephalins are also implicated in mediation of vomiting acting possibly at δ (CTZ) or μ (vomiting centre) opioid receptors. Substance P acting at neurokinin – 1 receptor in CTZ may also play a role. Table 1 shows the pathways for either stimulation of relay centers (CTZ, NTS) or VC or both and the types of receptors present which lead to vomiting.

Table 1: Receptors and pathways involved in stimulation of NTS, CTZ and Vomiting Centre and choice of drugs



Emetics

Emetics are drugs used to evoke vomiting when a toxic substance has been swallowed. They may either act directly (apomorphine) or reflexly on CTZ (Ipecacuanha). Apomorphine is a semisynthetic derivative acting as dopaminergic agonist on CTZ. Apomorphine (6mg) induces vomiting within 5-10 minutes when injected intramuscularly or subcutaneously. Ipecacuanha containing emetine is used as syrup (15-20 ml in adults). Copper sulphate,

powdered mustard suspension or oil or strong salt solution can also be used in emergency. They act through stimulation of receptors in stomach. Elimination of respiratory depression should be made before using the above drugs. Emetics are contraindicated in poisoning of any corrosive (danger of perforation), CNS stimulant (precipitation of convulsion), kerosene (aspiration pneumonia due to low viscosity), morphine or phenothiazine (emetics are ineffective) and in unconscious patients (danger of aspiration due to absence of laryngeal reflex).

Antiemetics

These drugs are generally employed for the treatment of nausea or vomiting induced by motion sickness, morning sickness, gastrointestinal disturbance, postoperative emesis, cytotoxic drug or radiation-evoked emesis. Variety of drugs, having different chemical and pharmacological profiles is useful antiemetic agents. They are classified as follows:

1. Antimuscarinic – Hyoscine, dicyclomine etc.
2. H₁-antihistaminics – Promethazine, Diphenhydramine dimenhydrinate, cyclizine, Meclizine, cinnarizine etc.
3. Neuroleptics – Chlorpromazine, prochlorperazine, haloperidol, droperidol etc.
4. Prokinetics- Metoclopramide, domperidone, cisapride etc.
5. 5HT₃ antagonist– Ondansetron, granisetron, bemesetron, renzapride, zacopride etc.
6. Miscellaneous – Dexamethasone, benzodiazepine, Cannabinoids etc.

1. Antimuscarinic drugs : Hyosine is used for prophylaxis as well as for the treatment of motion sickness. Administered in 0.2 – 0.4 mg dose either oral or intramuscular, it has got short duration of antiemetic action. It blocks the cholinergic pathway from vestibular apparatus to vomiting centre but is ineffective against drugs acting directly on CTZ. It produces side effects like drowsiness, dryness of mouth, blurring of vision and retention of urine.

Dyclomine is used in prophylaxis of motion sickness and morning sickness in oral doses of 10-20 mg per day.

2. H₁-antihistaminics : The use of H₁-antihistaminics is based on their central anticholinergic, antihistaminic and sedative properties. They are effective in vomiting due to motion sickness, Meniere's disease, pregnancy, uremia and postoperative emesis. Peripheral antimuscarinic action is also important for antiemetic effect. H₁-antihistaminics have little or no activity against substances inducing vomiting by acting directly on CTZ though they are effective in motion sickness and substances active locally in stomach to induce vomiting. These should be avoided in first trimester of pregnancy to avoid any foetal damage.

Promethazine theoclate (avomine, 25 mg Tab.) is especially promoted as antiemetic. It produces sedation and dryness of mouth. Cyclizine and meclizine are long acting antihistaminics and mainly used for sea sickness (24 hrs).

Cinnarazine is recently introduced anti-vertigo drug which has in addition to H₁-blocking property also inhibits influx of calcium from endolymph into the vestibular sensory cells which mediates labyrinthine reflexes. Drug used for motion sickness should be given half to one hour before journey.

3. Neuroleptics : They are potent drugs blocking D₂ receptors in CTZ. These are mainly used in chemotherapy-, post-anaesthetic-, disease-, malignancy- and radiation sickness-induced vomiting and vomiting in hyperemesis gravidarum. **They are not effective in motion sickness.**

Phenothiazines- the antiemetic dose of phenothiazines such as chlorpromazine, prochlorperazine is about 20-30% of their antipsychotic dosage whereas the dose for perphenazine is similar. They can cause significant degree of sedation and acute muscle dystonia in children specially girls.

Haloperidol and droperidol are mainly used to control postoperative vomiting and vomiting in patients on cancer chemotherapy.

4. Prokinetic drugs: They promote gastroduodenal peristalsis and speed gastric emptying.

Metoclopramide is chemically related to procainamide. It increases gastric peristalsis while relaxing pylorus and 1st part of duodenum. This is independent of vagal innervation but their action is more prominent when vagus is intact. On CTZ, it acts by selective blocking of D₂ receptor inhibiting apomorphine-induced vomiting. At the periphery it enhances Ach release causing gastric prokinetic effect and enhancing lower oesophageal sphincter tone. **Prokinetic action of metoclopramide is blocked by atropine.** At high doses it acts as 5HT₃ antagonist. It is rapidly absorbed orally, enters brain, crosses placenta and is secreted in milk. It causes sedation, dizziness, diarrhea and muscle dystonia. On long term use it can cause parkinsonism, galactorrhoea and gynaecomastia. It **should not** be used to augment lactation because it is secreted in milk.

It hastens absorption of many drugs like aspirin and diazepam (facilitating gastric emptying). It reduces the extent of absorption of digoxin by allowing less time for it. Bioavailability of cimetidine is also reduced. By blocking dopamine receptors in basal ganglia, it abolishes therapeutic effect of levodopa. It is used mainly as antiemetic, gastrokinetic in dyspepsia and GERD. It is administered in a dose of 10 mg three times a day orally (po) or intramuscularly (im). In children the dose is 0.25 to 0.5 mg/kg (po and im). It is available as 10 mg Tablet (Perinorm), 5 mg / 5 ml syrup, 10 mg/2 ml injection for oral or im use.

Domperidone is D₂ antagonist and is a lower efficacy antiemetic and prokinetic agent. **Prokinetic action is not blocked by atropine.** It crosses into CNS poorly (cf. CTZ which is outside the Blood Brain Barrier). Extra pyramidal side effects are rare but hyperprolactinemia can occur. Its efficacy is lower than metoclopramide. It is orally absorbed with bioavailability of 15% (1st pass metabolism) and its t_{1/2} is 7.5 hrs. It can cause cardiac arrhythmias on rapid I.V. injection (10-40 mg Tab.). Administered with levodopa and bromocriptine it counteracts their dose limiting emetic action without affecting the therapeutic effect in parkinsonism. Dose is 10-40 mg, three times a day in adult and 0.3 to 0.6 mg/kg in children.

Cisapride is a prokinetic agent which resembles metoclopramide but has **no central depressant or D₂ antagonist or any action on CTZ.** Its action is blocked by atropine. Cisapride stimulates 5HT₄ receptors and increases cAMP activity and releases Ach from myenteric plexus. Oral bioavailability is 33% and is primarily inactivated through liver. Its t_{1/2} is 10 hrs and dose should be reduced in liver diseases. It can cause arrhythmias with macrolides and imidazoles. Its main use is in gastroesophageal reflux disease. Dose is 10-20 mg, three times a day in adult.

5. 5HT₃ antagonist : Ondansetron and granisetron have been introduced for the control of cytotoxic-induced vomiting. Renzapride, zacopride, bemasetron, and tropisetron are recently introduced 5HT₃ antagonist used to prevent nausea and vomiting after cancer chemotherapy.

Ondansetron- It blocks the depolarizing action of 5HT through 5HT₃ receptors or vagal afferents in the GIT as well as in NTS and CTZ. It blocks the emetogenic impulses both of central and peripheral origin. Its oral bioavailability is 60-70% (1st pass metabolism). Its t_{1/2} is 3-5 hrs and duration of action varies from 4-12 hrs. It should be given half an hour before chemotherapeutic infusion as slow i.v. injection.

6. Miscellaneous: Cannabinoids- Nabilone, a synthetic cannabinol derivative is found to be effective against CTZ-stimulated vomiting. Its effect is blocked by naloxone. It is given orally. Its plasma half life is 120 min and is excreted both in urine and faeces. Unwanted effects include drowsiness, dry mouth, dizziness and postural hypotension.

Steroids like dexamethasone and methylprednisolone have antiemetic activity in high doses probably through inhibition of prostaglandin synthesis. Neurokinin-1 antagonists (Vofopitant, GR 05171) suppressing substance P can also act as an effective antiemetic agent.

Choice of antiemetic drugs

- H₁ receptor antagonist
 - Cyclizine – motion sickness
 - Promethazine – severe morning sickness of pregnancy and space motion sickness
 - Cinnarizine – Motion sickness, vestibular disorder (meniere's disease)
- Muscarinic receptors antagonists
 - Hyosine – Motion sickness
- D₂ receptor antagonists
 - Phenothiazines – Emesis induced by uraemia, radiation, viral gastroenteritis and severe morning sickness of pregnancy.
 - Metoclopramide – Emesis induced by uraemia, radiation, GI disorder, cytotoxic agents
- 5HT₃ antagonist
 - Ondansetron - Emesis induced by cytotoxic anti cancer drugs and radiation and postoperative vomiting
- Cannabinoids
 - Nabilone - Emesis induced by cytotoxic anticancer drugs

Drugs for Acid Peptic Diseases

Acid peptic disease includes peptic ulcer (gastric and duodenal), gastroesophageal reflux disease (GERD) and pathological hypersecretory states such as Zollinger-Ellison syndrome induced by gastrin secreting tumour.

Pathogenesis: Dyspepsia, in its various forms has been mankind's companion since the advent of bad cooking, overindulgence and anxiety. For several decades, the dictum "no acid-no ulcer" has dominated the pharmacological basis of treatment of ulcer therapy, and the drugs used, reduced acid secretion. However, in 40-70% patients of duodenal ulcer (DU), acid secretion is within normal limits, whereas in gastric ulcer (GU) acid secretion is either normal or below normal. Patients of Zollinger-Ellison syndrome, characterized by abnormally high acid secretion, show minimal incidence of peptic ulceration. It is therefore, apparent that peptic ulceration is not solely induced by offensive acid and pepsin secretion. Breakdown of mucosal resistance which constitute mucin bicarbonate secretion, phospholipids layer and tight junctions, cell proliferation, prostaglandins, epidermal growth factors, mucosal blood flow etc. have got an important role to play in ulcerogenesis Fig. 1). In a broad sense, ulcers are thought to be due to an imbalance between aggressive and defensive mucosal factors. The treatment of peptic ulcer disease is thus, directed towards strengthening the mucosal defensive factors rather reducing acid-pepsin activity.

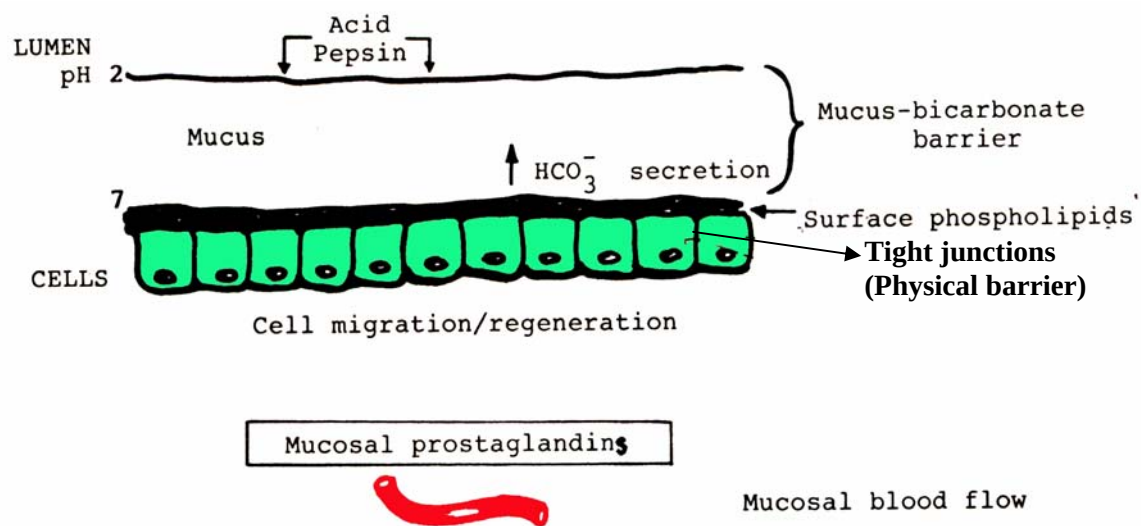


Fig.1: Gastric Mucosal Barriers

Acid-pepsin secretion

The stomach secretes about 2500 ml of gastric juice per day which consists mainly of hydrochloric acid (HCl) and pepsinogen as the principal gastric secretory product. HCl is directly secreted in the lumen by the parietal cells where H⁺ and Cl⁻ ions combine to form HCl (Fig. 2). The other important cell type, the chief cells secrete pepsinogen which is activated into pepsin in the acid medium (below pH 4). Acidification of ingested food initiates the process of digestion by creating optimal conditions for peptic digestion of proteins. Stimulation of gastric secretion during digestion involves cephalic, gastric and intestinal phases which overlap in time and are modulated by complex neural and humoral interplay.

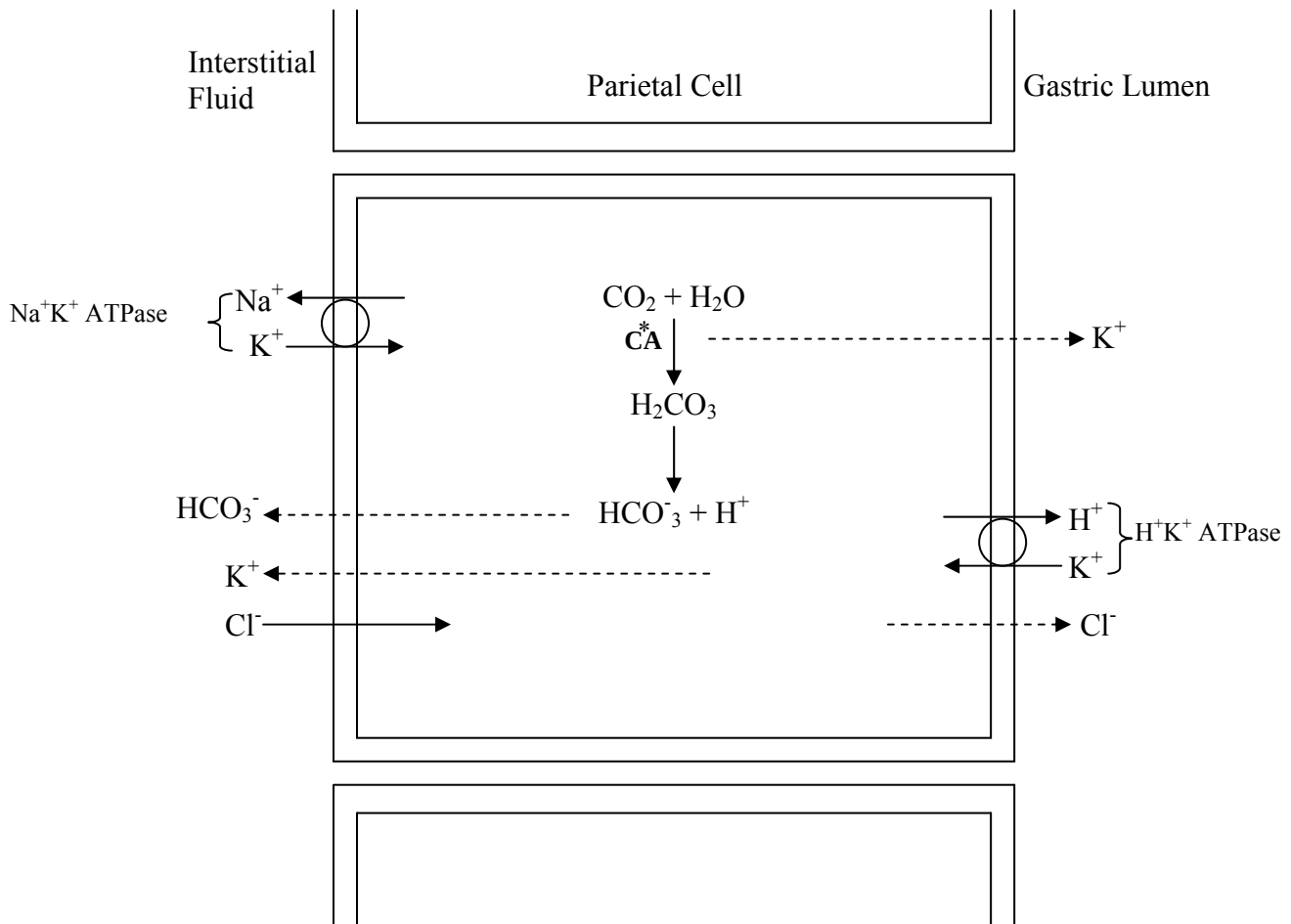


Fig. 2: Secretion of HCl
*CA – Carbonic anhydrase

At rest parietal cells contain abundant tubulovesicular structures with H^+K^+ ATPase molecules within their walls. When stimulated, these tubulovesicular structures move to the apical membrane and fuse, thus inserting many molecules of H^+K^+ ATPase into the membrane. These ATPase molecules are now exposed to K^+ in the extracellular fluid, and H^+ , K^+ exchange begins. H^+K^+ ATPase in the apical membrane of the parietal cell pumps H^+ against the concentration gradient. Acid secretion is stimulated by histamine via H_2 receptors (parietal cells) and by ACh via M_1 (enterochromaffin-like cells (ECL) secreting histamine) and M_3 (parietal cells) receptors. Gastrin probably acts directly (parietal cells) although mainly through enterochromaffin-like (ECL) cells via G receptors. Prostaglandins (PGs), PGE and PGI_2 , on the other hand, inhibit gastric acid secretion through stimulation of PG receptors. H_2 receptors activate H^+K^+ ATPase by generating cAMP, while muscarinic and gastrin receptors appear to function through the phospholipase C, leading to mobilization of intracellular Ca^{++} . Prostaglandins decrease adenyl cyclase activity and reduce cAMP levels to inhibit acid secretion (Fig. 3).

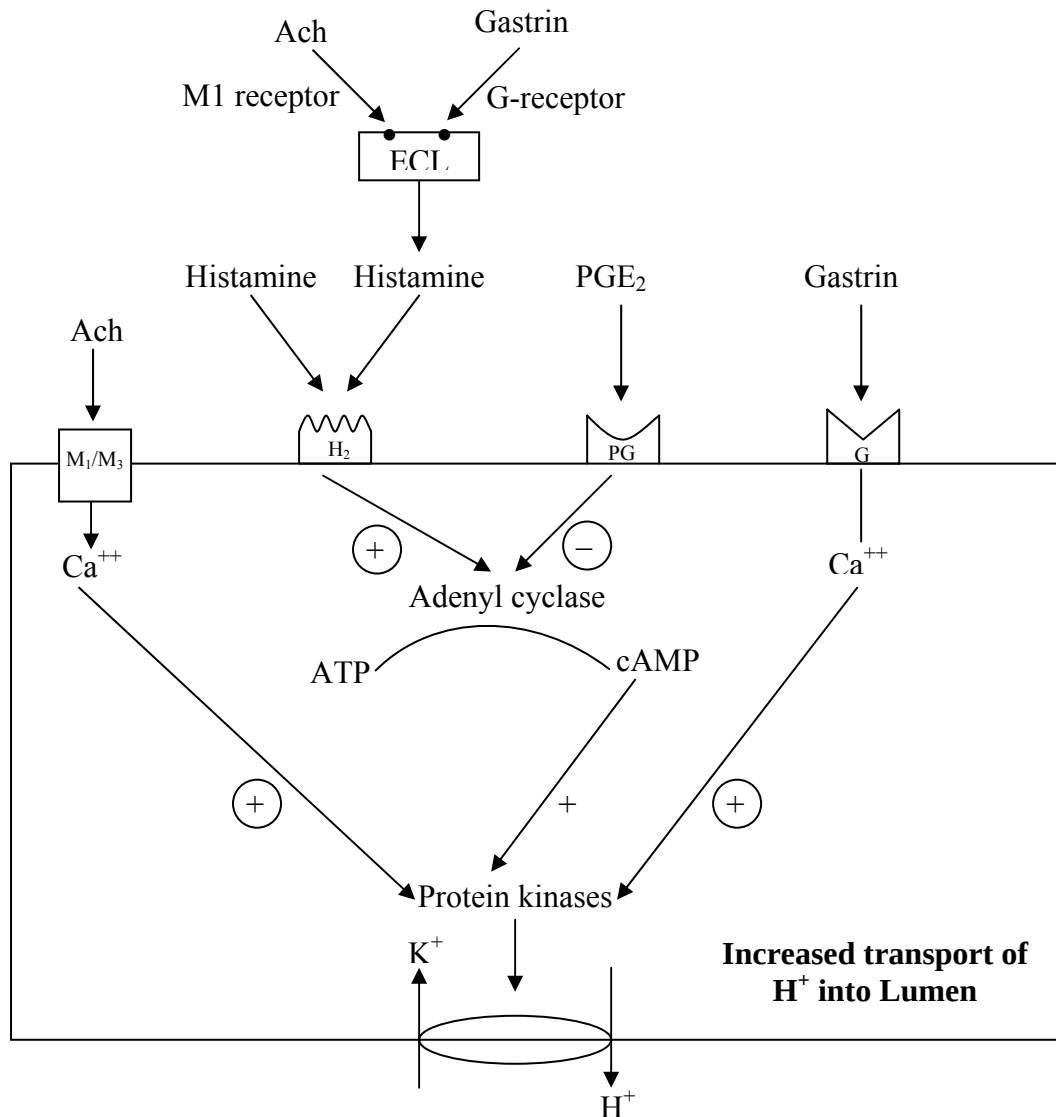


Fig. 3: Mechanism of Gastric secretion

Mucosal barrier

The mucosal barrier consists mainly of mucous and bicarbonate (HCO_3^-) secreted by neck cells of gastric glands and surface mucosal cells. Mucous is one of the nature's perfections, protecting the gastrointestinal tract from infective, chemical and physical insults. It has been commented that it encloses the gastric juice in the stomach as if it is an impermeable porcelain vase. Much of the HCO_3^- is trapped in the mucous gel and both together help in maintaining the pH gradient of 1-2 at the luminal side and 6-7 at the surface of the epithelial cells. PGs stimulate mucous and HCO_3^- secretion and also increase the mucosal blood flow. Epithelial protection also involves through tight junctions that serve as a physical barrier through ion permeation and by virtue of rapid cell proliferation, cell restitution and surface active phospholipids layer (Fig. 1). The duodenum is also protected by this mucosal barrier from the effects of HCl.

A principal role of *Helicobacter pylori* in ulcer pathogenesis is now widely accepted. The bacterium is believed to colonize the mucus overlying gastroduodenal epithelium and lower

the resistance of the mucosa to offensive acid-pepsin assault. Eradication of this bacterium has been shown to reduce ulcer recurrence. Chronic *H. pylori* infection can lead to antral and corpus atrophic gastritis leading to duodenal and gastric ulcers in later stages. It can also lead to gastric dysplasia and cancer.

Salicylates and other nonsteroidal anti-inflammatory drugs (NSAIDs) may not only cause dyspepsia but also cause or exacerbate peptic ulcers and their complications. NSAID-induced ulcers occurs both when taken orally or parenterally. They increase HCl secretion and decrease epithelial cell proliferation. NSAIDs cause injury by inhibition of prostaglandins (PGs) synthesis which have protective role as PGs (PGE and PGI₂) increase mucin, surface active phospholipid and bicarbonate secretion and mucosal blood flow affording cytoprotective action. However, taken orally, NSAIDs at gastric pH are mainly unionized so they are absorbed from the stomach mucosal cells and become ionized inside the mucosal cells where the pH is generally around 7 leading to its precipitation thereby causing ion trapping and cell damage while, parenteral NSAIDs mainly affect cytoprotective action of the PGs only.

Ulcer is any disruption in continuity of the mucosal integrity generally more than 5mm in size and deep involving submucosal layer. Burning epigastric pain, exacerbated by fasting and improved with meals, comprises of a symptom complex which is known as peptic ulcer disease. These ulcers are of two types

1. Duodenal ulcer – Mainly caused by *H. pylori*, NSAID-induced (basal and nocturnal acid secretion increased and HCO₃⁻ decreased).
2. Gastric ulcer – Mainly caused by mucosal injury (basal and stimulated acid secretion decreased).

Drugs Used In Acid Peptic Disorder

Drugs used in acid peptic disorder can be classified according to their mode/mechanism of action:

i) By neutralization of acid secretion (Ant-acid)

- a) Systemic – Sodium bicarbonate, Sodium citrate
- b) Non-systemic – Magnesium hydroxide, magnesium carbonate, magnesium trisilicate, aluminium hydroxide gel, megaldrate, calcium carbonate

ii) By reduction of gastric acid secretion

- a) H₂ antihistaminics – Cimetidine, ranitidine, famotidine, roxatidine, nizatidine
- b) Proton pump inhibitors – Omeprazole, pantoprazole. Lansoprazole, esomeprazole
- c) Anticholinergics – Pirenzepine, telenzepine, dicyclomine, propantheline, oxyphenonium, doxapin, trimipramine
- d) Prostaglandins – Misoprostol, enprostil, rioprostil, arboprostil
- e) Anti-gastrin – Octreotide

iii) Mucosal protective/defensive factor promoting agents

- a) Ulcer protectives – Sucralfate, colloidal bismuth subcitrate
- b) Ulcer healing drugs – Carbenoxolone sodium, deglycerrhized liquorice
- c) Prostaglandins – Misoprostol, enprostil, rioprostil, arboprostil

d) Low dose antacid – Aluminium hydroxide

iv) **Anti *H. Pylori* agents** – Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline, colloidal bismuth subcitrate

Antacids

Antacids are weak bases that neutralize gastric acid, raise pH of gastric contents (optimum peptic activity between pH 2-4). The beneficial effect of antacids can also be due to their mucosal-protecting actions such as stimulation of bicarbonate production, enhancement of PG synthesis or reduction of *H. pylori* colonization. The potency of antacids is determined by acid neutralizing capability (ANC) i.e. number of mEq of HCl that is brought to pH 3.5 in 15 minutes by unit dose of antacid preparation.

Systemic antacids: NaHCO_3 is water soluble, short acting and acts instantly. It is a potent neutralizer (ANC- 12 mEq HCl/g). pH may rise above 7 which can cause dramatic acid rebound phenomenon, alkalosis and CO_2 accumulation in stomach. Increase Na^+ load can cause water retention so it is contraindicated in chronic cardiac failure patients. These can be used in patients of dyspepsia and can give symptomatic relief in peptic ulcer and reflux diseases.

Non systemic antacids: These are insoluble in water and are poorly absorbed, form chloride salt in stomach and in turn reacts with intestinal HCO_3^- so that there is no final acid base disturbance. Mg^{2+} salts absorb water, stimulate cholecystokinin and thus promote laxative action (ANC– 10-30 mEq HCl/g). Al^{3+} salt polymerizes in itself and coats the ulcer crater, relaxes intestine (constipation), adsorbs pepsin at pH >3 and inactivates it (ANC– 1-2.5 mEq HCl/g). Hypophosphatemia can cause osteomalacia and stone formation so it is contraindicated in renal failure. Calcium carbonate is a potent neutralizer (ANC– 20 mEq HCl/g). The major drawback being Ca^{2+} diffuses in GI mucosa which causes direct stimulation of parietal cells for HCl and gastrin secretion. There is rebound hyperacidity that increases the antacid requirement. In addition, it causes hypercalcemia, hypercalciuria, alkalosis and stones. So these are contraindicated in renal failure.

Antacid combinations preferable: Fast (Mg^{2+}) and slow (Al^{3+}): Mg^{2+} (laxative) and Al^{3+} (constipating). This can decrease the dose and toxicity of individual component.

Milk alkali syndrome: Earlier calcium carbonate was advocated with large doses of milk that led to milk alkali syndrome which comprises of headache, dizziness, anorexia, weakness and abdominal discomfort, Ca deposits and renal stones.

Administration: Sufficient dose of antacids when given 1 hr after meal effectively neutralize gastric acid for 2 hr and a second dose is given after 2 hr maintains the effect for over 4 hr after meals. Different doses of antacids are required depending upon their ANC.

Uses: Antacids are mainly used in treating GERD or relieving pain from episodes of heartburn and nonulcer dyspepsia. They are also used as adjuvants with antisecretory agents in treating ulcer dyspepsias.

Gastric Antisecretory Drugs

Gastric acid secretion is under the control of three prominent secretagogues viz histamine, acetylcholine and gastrin. However, the final common pathway is through the proton pump, H^+/K^+ ATPase.

H₂-Receptor antagonist : Cimetidine, ranitidine, famotidine and roxatidine, the four H₂-antagonists are available in India. These drugs share structural homology with histamine although each has different potency, inhibiting all phases of gastric secretion, fasting and nocturnal as well as histamine- and food-stimulated acid secretion. They partially decrease gastrin- and cholinergic-stimulated acid secretion. Secretory responses to other stimuli like insulin and alcohol are also attenuated. Acid volume, pepsin content and intrinsic factor are reduced but vitamin B₁₂ absorption is not interfered with. They have got anti-ulcerogenic effect against gastric ulcers induced by stress and NSAIDs.

All are absorbed orally with famotidine having lowest bioavailability (40%), Ranitidine (50%), cimetidine (80%) and Nizatidine having highest bioavailability (>90%). Cimetidine undergoes 1st pass metabolism. Food does not affect their absorption. The relative potency varies from cimetidine (1) to famotidine (32) with ranitidine and nizatidine having intermediate potency. Cimetidine can cross placenta and brain while, others have poor penetrability. Their $t^{1/2}$ varies from 1.5 – 4 hr and duration of action varies from 6-12 hr the highest being with famotidine.

The common side effects mostly found with cimetidine are headache, dizziness, diarrhoea, muscle pain. When given as intravenous bolus, cimetidine mainly causes bradycardia, arrhythmias and cardiac arrest. Fever, transient neutropenia and rashes are infrequent. Elevation of plasma amino-transferases can also occur. Cimetidine has got a prominent antiandrogenic effect. It produces reversible gynaecomastia in males due to enhanced release of prolactin when given in high doses and for long duration.

The major drug interactions of H₂-blockers occur with antacids which decrease their absorption. Cimetidine inhibits cytochrome P₄₅₀ which leads to inhibition of metabolism of phenytoin, phenobarbitone, sulphonylureas, theophylline, metronidazole, warfarin, quinidine, lignocaine, nifedipine etc. It also inhibits renal tubular secretion of procainamide and decreases absorption of ketoconazole. Cimetidine therefore, is not commonly used because of low potency and many side effects and drug interactions with large number of drugs affecting their metabolism through inhibition of cytochrome P₄₅₀ activity.

The advantage of ranitidine over cimetidine is that it is 5 times more potent than cimetidine with minimal cytochrome P₄₅₀ inhibition, permeability to cross blood brain and placental barrier and antiandrogenic activity. It has also got a longer duration of action than cimetidine. The newer congeners (famotidine and roxatidine) have got much less side effects and are more potent. Suppression of nocturnal acid secretion appears to be the most important determinant of rate of healing of duodenal ulcer. Further to prevent recurrence, half of the daily dose of H₂-blocker can be given daily at bed time (HS). The initial recommended dosing profile of cimetidine is 400 mg bid, Ranitidine 300 mg HS, famotidine 40 mg HS and nizatidine 300 mg HS.

These drugs are mainly used for duodenal, gastric and stress ulcers, ZE syndrome and gastro esophageal reflux disease (GERD). They can also be used as adjuvant in therapy of urticaria not responding properly with H₁-blocker and as prophylactic to prevent aspiration pneumonia.

Proton pump inhibitors (PPI) : These are substituted benzimidazole derivatives that covalently bind and irreversibly inhibit H⁺, K⁺ ATPase. Both basal and stimulated acid secretion to various secretagogues is inhibited. They inhibit the final common step in gastric

acid secretion dose-dependently. Esomeprazole, the newer agent is a racemic mixture. Omeprazole, lansoprazole and rabeprazole are available as enteric coated granules in a sustained release capsule that dissolves within the small intestine at pH 6. Pantoprazole is also available in parenteral formulation.

Omeprazole is a pro drug. It is degraded at low pH. It is absorbed in intestine and absorption is around 50% after oral administration. It is highly protein bound and $t^{1/2}$ ranges from 1-2 hr. It is inactive at neutral pH, but its accumulation in an acidic environment in the gastric canaliculi activates it, probably by protonation. Its inhibitory action on acid secretion improves its own relative bioavailability. At pH <5, it rearranges into 2 charged cationic forms (a sulphenic acid and a sulphenamide configurations) that react covalently with the SH group of H^+K^+ ATPase and inactivate it irreversibly. Adverse effects are relatively uncommon on short term use while, long term use may cause severe hypochlorhydria which may favour bacterial overgrowth, hypergastrinemia inducing gastric hyperplasia. They inhibit oxidation of certain drugs like diazepam, phenytoin, warfarin and increase their plasma levels.

Newer PPIs are developed either for their reversible proton pump inhibitory activity or resistance to acid degradation on oral administration. Lansoprazole inhibition is partly reversible while, pantoprazole is more acid stable. Rabeprazole and esomeprazole seem to be better ulcer healers. The recommended dose profile is 20-40 mg/day for omeprazole, 30-60 mg/day for lansoprazole and 40 mg/day for pantoprazole. They are either given in two divided doses, first dose in the morning one hour before meal and the second dose at bed time or as a single full dose at bed time for 4-6 weeks. However as a maintenance dose for prevention of remissions, the dose can be reduced to half at bed time. PPIs are mainly used for ZE Syndrome, duodenal ulcer, GERD and *H pylori* therapy.

Anticholinergics: Pirenzepine is a relatively specific M_1 -receptor antagonist and acts at M_1 receptor found in the intramural ganglia, histamine secreting cells and gastric parietal cells. It reduces basal and stimulated acid secretion at doses that have minimal effect on heart, eyes, bladder etc. It is given orally and is equally effective as cimetidine in healing gastric and duodenal ulcer. Blockade of ganglionic receptors also appear to underlie the ability of pirenzepine to inhibit relaxation of lower esophageal sphincter. It may produce unwanted effects like dry mouth and blurring of vision.

Antigastrin: Octreotide is a long acting synthetic somatostatin analogue and inhibits gastric and pancreatic secretion. It is reported to be effective against ZE syndrome.

Prostaglandin analogues: PGE_2 and I_2 inhibit acid secretion and promote mucus and HCO_3^- secretion. In addition, they have got cytoprotective action and reinforce the mucus layer by increasing phospholipids content of surface epithelium, mucosal repair and restitution and mucosal blood flow. These drugs combine with the PG receptor on the parietal cell and inhibit the action of cAMP. Misoprostol (15-methyl PGE_1) is rapidly absorbed, undergoes extensive 1st pass metabolism and is converted into active misoprostolic acid. It is approved by the US Food and Drug Administration for Clinical use in the prevention of NSAID induced gastroduodenal mucosal injury. The standard therapeutic dose is 200 μ g, 6 hourly for 2 to 3 weeks. The major adverse effect includes nausea, diarrhea, abdominal cramps and dysmenorrhoea. PGs should be avoided in pregnancy as it can lead to abortion.

Other synthetic PGs used are enprostil (dehydro PGE₂), rioprostil (methyl PGE₁) and arboprostil (15 methyl PGE₂).

Ulcer protectives: Sucralfate is basic Al³⁺ salt of sulfated sucrose. It polymerizes at pH 4 forming a gel which binds to proteins and glycoproteins in the ulcer crater and forms a protective coating which acts as a barrier to acid, pepsin and bile salts. It has no acid neutralizing property but adsorbs pepsin and bile salts. It enhances cytoprotection by augmenting gastric mucosal PGs synthesis. Sucralfate may also induce a trophic effect by binding EGF, stimulate mucus and HCO₃⁻ secretion and enhanced mucosal defense and repair. It is minimally absorbed after oral administration. The most common adverse effect is constipation (2-3%) and hypophosphatemia. It should be avoided in chronic renal insufficiency to prevent aluminum induced neurotoxicity. Standard dosing is 1 g, four times a day. As sucralfate adsorbs many drugs like digoxin, warfarin and tetracyclins so it should be taken 2 hours after the consumption of these drugs.

Colloidal bismuth subcitrate (CBS) and tripotassium dicitratobismuthate are the most widely used preparations of bismuth. It does not act as antacid but heals 60% ulcers at 3-4 weeks and 80-90% at 6-8 weeks of its daily treatment. They are reported to be effective against *H. pylori* and together with tetracyclines, metronidazole and antisecretory drugs like PPI or H₂-blocker therapy, is reported to increase ulcer healing upto 98% and prevent gastric/duodenal ulcer relapse from 80% to nearly 10%. CBS combines with mucus at the ulcer base forming a glycoprotein bicomplex that coats the ulcer, adsorbing pepsin, enhancing local PG synthesis and stimulating bicarbonate secretion. CBS is minimally absorbed after oral administration and whatever small amount is absorbed, is excreted in the urine. Unwanted effects include nausea and vomiting and blackening of tongue and faeces. Prolonged use can cause osteodystrophy, encephalopathy if renal excretion of bismuth is impaired.

Dose- 120 mg 6 hourly

Ulcer healing agents: Carbenoxolone and deglycerrizinated liquorice are derivative of glycyrrhizic acid, a component of liquorice roots are found to promote healing of gastric and duodenal ulcers by altering the composition and quantity of mucin. It is a steroid congener having aldosterone like activity increasing fluid retention and hypertension and hypokalemia. Concurrent administration of spironolactone, an aldosterone antagonist controls fluid retention as well as abolishes the ulcer healing effect of carbenoxolone, therefore its use is very limited. Deglycerrizinated liquorice (DGL) seems to have less fluid retention property compared to carbenoxolone.

Dose- carbenoxolone 100 mg/8 hourly, DGL 400 mg/6 hourly .

H. pylori regimens: *H. pylori* is a gram negative rod residing in deeper portion of mucus gel between the mucus layer and epithelium. It is S-shaped having multiple flagella. In developing countries, 80% of the population above the age of 20 may be affected. The colonization is influenced by domestic crowding, unsanitary condition, unclean food and water, exposure to gastric contents and is transmitted by oral-oral or faeco-oral route. The host factors like the duration and site of infection, the extent of inflammatory response and bacterial factors like structure, adhesions, porins and enzymes liberated govern the infectivity. *H. pylori* is generally associated with chronic active gastritis, duodenal ulcers, gastric adenocarcinoma and B-cell lymphoma but only 10-15% cause frank peptic ulcer.

The treatment is not straight forward, single antibiotic regimen is ineffective, addition of proton pump inhibitor or H₂ receptor antagonist enhances effectiveness of regimen probably

by altering acid environment and having direct inhibitory effect. At least 10-14 days of treatment is always better than short term treatment of few days. Documented eradication of *H. pylori* in patients with peptic ulcer disease is associated with dramatic decrease in ulcer recurrence to 4% in gastric ulcer patients and 6% in duodenal ulcer patients and may lead to diminished recurrence bleeding.

Triple Therapy

Lansoprazole 30 mg BD or ranitidine 300 mg OD or bismuth subcitrate 120 mg QID plus any 2 of (i) Amoxicillin 500 mg TDS, (ii) Clarithromycin 500 mg BD and (iii) Metronidazole 400 mg QID/tinidazole 500 mg BD.

Quadruple therapy

Omeprazole 40 mg BD + Tetracyclin hydrochloride 500 mg QID + Bismuth subcitrate 120 mg QID + Metronidazole 500 mg TDS

Prevention of ulcer relapse and complications

Following are the criteria which are important for the maintenance of ulcer therapy:

1. Frequent relapses
2. Severe and or prolonged pain with relapse
3. Previous haemorrhage or perforation
4. Other serious illnesses (cardiopulmonary disease)
5. Age over 60 yrs. (smoking etc as risk factors)
6. Large or deep duodenal ulcer at endoscopy
7. Need for NSAIDs with a known previous ulcer
8. Ulcer associated with NSAID medication

Various strategies to contain the remissions are advocated which include continuous or on demand intermittently low doses of H₂-blocker/ PPI or sucralfate or antacids. However, the continuous maintenance with low doses of H₂-blocker/ PPI is most effective and convenient.

Purgatives and Antidiarrhoeal Drugs

Diarrhoea and constipation are very common disorders of gastrointestinal tract (GIT) which although seem to be a part of our day to day life but can prove to be very severe or life threatening exacting an enormous toll in terms of morbidity and loss of work productivity. Worldwide more than 1 billion people suffer one or the other day from acute diarrhea every year. The fact that even a mild symptom may signal a serious underlying gastrointestinal lesion such as colorectal cancer or systemic disorder, becomes very important for a clinician. Better appreciation and knowledge of the pathobiology and pathophysiology is of importance in directing therapy for treatment of diarrhea as improper treatment strategy is detrimental to the health.

GIT is in a state of continuous contractile and secretory activity which is controlled by the enteric nervous system (ENS), central nervous system (CNS) and through their own muscular system, although most of the functions of GIT are autonomous which is controlled mainly by ENS. The ENS is connected to CNS by the sympathetic and parasympathetic system.

Numerous neurotransmitters like acetylcholine (Ach), amines (noradrenaline / 5-hydroxytryptamine), GABA, purines (ATP), gases (NO, CO) and different peptides help in the functioning of GIT.

The small intestine and colon have intrinsic and extrinsic innervation. The intrinsic system also called myenteric plexus or Auerbach's plexus is directed for controlling the motor function. The extrinsic system has a dual exchange innervation of both parasympathetic (Ach) which increases the activity of intestinal smooth muscles and sympathetic (NA) which decreases the activity of smooth muscle but causing the sphincters to contract.

Peristalsis is a reflex response occurring in all parts of GIT due to the stretch of the gut wall by the contents of lumen. The anterograde and retrograde release of neurotransmitters helps in the progression of peristalsis. Basic electrical activity (BER) is present in all parts of GIT except esophagus and proximal part of stomach and helps in coordinating the peristalsis and motor activity. Vagotomy makes peristalsis irregular. Migrating myoelectric complex refers to the electrical activity of GIT and migratory motor complex (MMC) refers to the accompanying contraction. MMC occurs in fasting state to get rid of the debris (house keeper) and occurs at the rate of 5 cm/min, at an interval of 90 min during which the gastric secretion, bile flow and pancreatic secretion are all increased. In humans there is a fed pattern of contractions (12 to 15/min) consisting of both propulsive and mixing movements. The gastric motility is characterized by a receptive relaxation activity and peristalsis begins in the lower portion of stomach (mixing and grinding). The contraction of the distal part of stomach is called antral systole. Gastric emptying is accomplished by the combined contraction of antrum, pylorus and upper duodenum acting as a unit. The tone of lower esophageal sphincter (LES) is under normal control of Ach (contraction) and NO/VIP (relaxation). Intestinal motility (12 BER cycles/min) comprises of, peristalsis, segmentation (to and fro movement) and tonic and prolonged contractions for greater exposure of the food contents. The colonic motility is characterized by the gastro-ileal reflex, peristalsis, segmentation and mass action contraction (movement from one portion of colon to another).

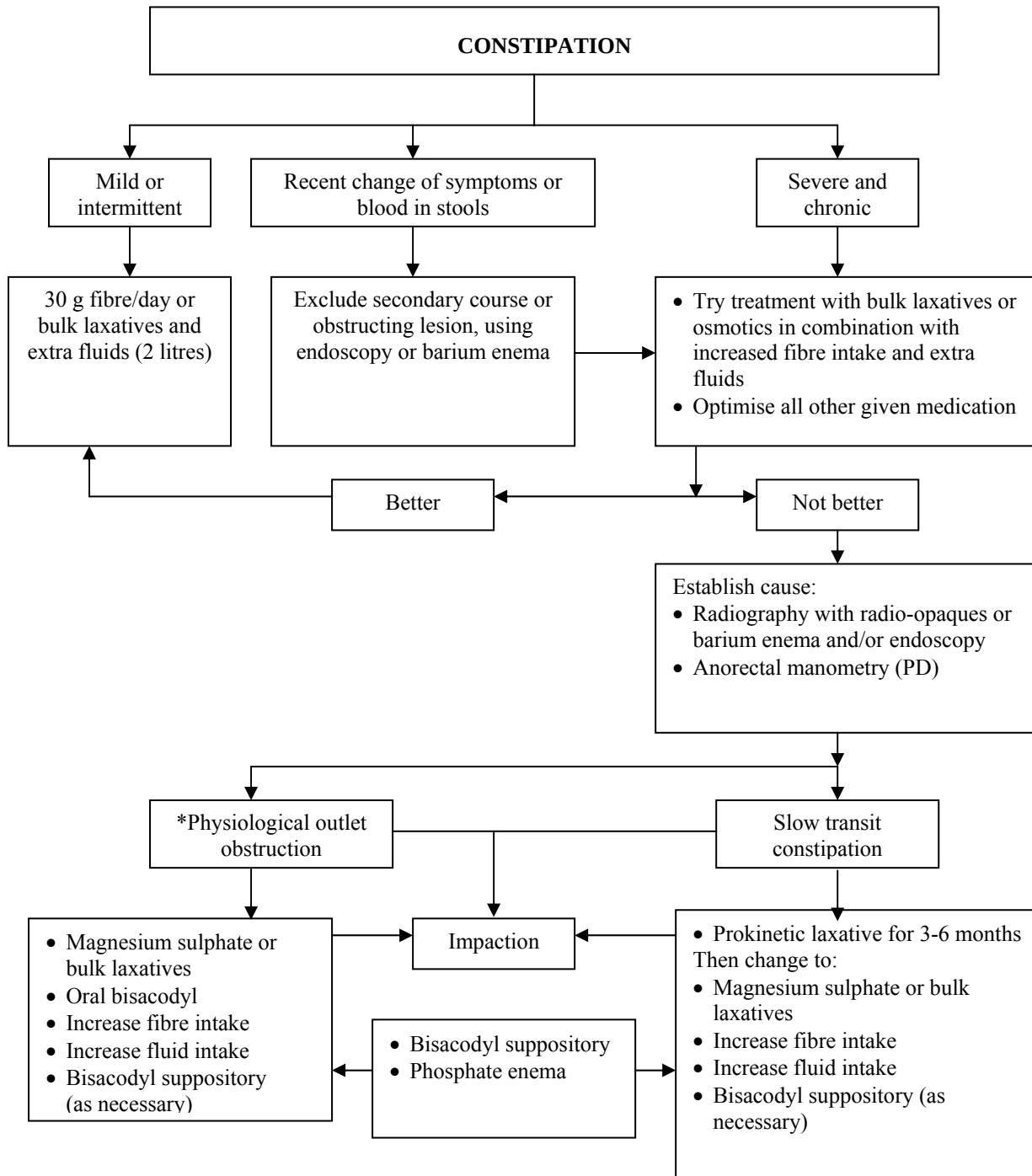
Constipation

The colon has a function of solidification, storage and proper and timely evacuation of faeces. The efficiency is determined by the nature of luminal contents, the normal colonic absorption and the neuromuscular function.

Constipation is derived from the Latin word "Con" – together, "Stipase" – to cram or pack. The normal stool frequency varies from 3 times per day to 3 times per week. Thus, the definition of constipation differs from people to people but constipation can be identified by symptoms like decreased frequency, difficulty in the initiation and passage of stools, incomplete evacuation and formation of firm and small amount of faeces. Constipation can be caused by lack of dietary fibres, certain drugs (opioids), hormonal (autonomic dysfunction) and certain systemic illnesses. Prolonged chronic constipation can be caused by slow transit idiopathic disorders, colonic inertia, outlet disorders and certain neurogenic conditions.

Constipation can be treated by increasing the fibre content of diet (20 to 30 g daily), taking plenty of fluids, appropriate bowel habit and training and giving attention to certain psychosocial and emotional factors. If the above modifications are insufficient then bulk forming agents should be the second line preference. Stimulants should be used at last with least effective dose and for short period of time. Table 2 gives the flow chart for the treatment of constipation.

Table 2: Flow chart of treatment of constipation



Purgatives

Laxatives / aperients are agents having milder action and helps in elimination of soft but formed stools. Purgatives / cathartics are agents having stronger action resulting in more fluid evacuation.

Classification

I. Luminally active agents

- i) Bulk forming - Dietary fibre, psyllium, ispaghula, methyl cellulose
- ii) Stoolsoftener - Dioctyl sodium sulphosuccinate (Docusates, Doss)
- iii) Lubricants - Liquid paraffin
- iv) Osmotic - Magnesium sulphate, magnesium hydroxide, sodium sulphate, sodium potassium tartrate, lactulose, sorbitol, mannitol, polyethylene glycol (PEG)

II. Stimulant (Contact) Purgatives

- i) Diphenylmethanes - Phenolphthalein, bisacodyl
- ii) Anthraquinones - Senna, cascara, rhubarb, aloes, danthron
- iii) Fixed oil - Castor oil

III. Prokinetic agents

- 5 HT₄ agonists e.g. Tegaserod
- Opioid receptor antagonists

Bulk Forming: These agents increase the stool mass. Fermentation produces short chain fatty acids which have got prokinetic action. These are contra-indicated in obstructive cases and in patients with megacolon and mega rectum. They cause bloating and abdominal pain. They can increase the Ca²⁺ load if agents like calcium polycarbophils are used. Sugar containing agents can cause intolerance in diabetics.

Softeners: These are anionic surfactants which lower the surface tension of stool and allow mixing of aqueous and fatty substances thereby softening the stools and allowing easier defaecation. They also increase the cyclic AMP and water secretion.

Osmotic agents : Osmotically mediated water retention can induce peristalsis and prompt catharsis. They may increase nitric oxide synthase and platelet activating factor. There is also production of inflammatory ionic mediator e.g. Mg²⁺. They are avoided in small children, and in patients with poor renal function. They can cause heart block, neuromuscular block, CNS depression and fluid and electrolyte imbalance.

Lactulose contains non-absorbable sugars, which draws water into the lumen. Its fermentation can lead to formation of lactic and acetic acids which are osmotic laxatives and stimulate motility. 15 to 20 ml of 70% solution is used at night and effect is seen after 24 to 48 hours. Lactulose finds important place in treatment of hepatic encephalopathy as it reduces blood ammonia concentrations. 2-3 soft stool evacuation/day at pH of 5.5 is required for its beneficial effects. It is also used in constipation caused by opioids, vincristine, in elderly and debilitated patients. Lactulose can cause flatulence, cramps, diarrhea etc.

PEGs are nowadays used in small doses to treat difficult cases of constipation. They are highly osmotically active.

Lubricants: They are viscous liquids which are pharmacologically inert and help in easy passage of stool by coating them. Because of their various side effects and irritant nature they are occasionally used nowadays especially in post operative patients.

Stimulants : These agents have direct effect on enterocytes, neurons, and muscles. They induce low grade inflammation and cause accumulation of water and electrolytes and

stimulate intestinal motility by release of mediators like prostaglandins, cAMP, nitric oxide (NO), cGMP and inhibition of $\text{Na}^+ \text{K}^+$ ATPase. Larger purgation can cause fluid and electrolyte imbalance and hypokalemia. They are routinely used in colonic atony. They can reflexly stimulate the gravid uterus and are contraindicated in pregnancy and obstructive disorders.

Bisacodyl is given in the dose 10-15 mg in adults and 5-10 mg in children (6-12 years). Enteric coated preparation are used once daily at bed time. Evacuation occurs in 6-8 hours i.e. in the morning. Rectal preparations cause catharsis in 30-60 min. Phenolphthalein is withdrawn from the market because of carcinogenicity seen in mouse.

Castor oil is one of the oldest remedies obtained from seeds of *Ricinus communis*. It has recently lost its usage because of irritant nature and due to side effects of stronger purgation. It contains triglyceride of ricinoleic acid which is a long chain fatty acid and polar in nature. It is hydrolysed to ricinoleic acid and glycerol by pancreatic lipase. Ricinoleic acid is absorbed poorly. It irritates the mucosa and stimulates small intestinal contractions. Most importantly they decrease intestinal absorption of water and electrolytes. Adult dose- 15-25 ml of castor oil may be taken in the morning. It causes purgation within 2-3 hours.

Newer and more potent prokinetic agents like tegaserod may be useful for the treatment of chronic constipation. Prostaglandin analogues like misoprostol and RU-0211 (under trial) stimulate colonic contraction. Other agent like colchicine has also been shown to be effective in constipation. A novel biologic agent, neurotrophin-3 has shown to be effective in improving the stool consistency and frequency by some unknown mechanism.

Enemas are employed by the individual themselves or as adjuncts to bowel preparation to empty the distal colon and rectum of the faecal matter. Some enemas may contain additional substances which are osmotically active or irritants. Repeated enemas should be avoided as they can cause hyponatremia and hypocalcemia specially with the phosphate enemas. Glycerin (trihydroxy alcohol) is used only rectally and is given in a single daily dose as a 2 or 3 g rectal suppository or as 5 to 15 ml of 80% solution in enema form.

Laxatives should not be used in patients of undiagnosed abdominal pain and vomiting. They should be avoided in secondary constipation due to stricture or obstruction in bowel, hypothyroidism, hypercalcemia and malignancies.

Uses:

- (i) Functional constipation
- (ii) Spastic and atonic conditions
- (iii) Bed ridden and postoperative patients to avoid straining at stools
- (iv) Preparation of bowel before surgery
- (v) Food and drug poisoning and in worm infestations

Requirement of soft formed faeces takes 1-3 days and agents like bulk forming, docusates, lactulose can be used. Semi fluid stools within 6-8 hours can be formed by agents like bisacodyl and senna and other stimulants. Watery evacuation within 1-3 hours can be done by agents like saline purgatives and castor oil.

Purgative Abuse

It is a psychological problem and drugs used or misused to get full evacuation. The dangers associated can be flaring of intestinal pathology, rupture of inflamed appendix, fluid-electrolyte imbalance, steatorrhea and malabsorption syndromes, protein losing enteropathy and spastic colitis.

Diarrhoea

In Latin “Dia” means through and “Rhoein” means to flow or to run. Diarrhoea is defined as excessive fluid weight with 200 g/day representing the upper limit of normal stool water weight in healthy adults. Fluid content is a major determinant of the stool volume and comprises of 70 to 80% of total stool weight. About 8 to 9 liters of water enters the intestine per day but only 1-1.5 liters crosses the ileo-caecal valve and about 100 ml constitutes the faeces. The maximum absorption capacity of small bowel is 16 litres and that of colon is 5 to 6 liters. Decreased absorption of water or increased gastrointestinal motility can cause diarrhea.

The recent change in the consistency of the stool is more characteristic rather than the number that is important. Diarrhoea can be acute (<2 weeks), persistent (>2 weeks) and chronic (>4 weeks). The mechanism can be either the increased osmotic load in the intestine (presence of non absorbable solutes), excessive secretion of water and electrolytes into the lumen, exudation of protein and fluid from the GI mucosa or the increased motility of the intestine (rapid transit).

The jejunum is freely permeable to salt and water (along with glucose and aminoacids). In the ileum and colon, salt and water absorption is mediated by $\text{Na}^+ \text{K}^+$ ATPase pump present at the basolateral membrane. There is glucose facilitated sodium absorption (1 Na^+ along with 1 glucose molecule). This is also the basis of oral rehydration therapy (ORT) which remains intact even in the severe cases. A variety of neural and non-neural mediators regulate colonic fluid and electrolyte balance including cholinergic, adrenergic and serotonergic mediators. Angiotensin and aldosterone also influence colonic absorption.

Acute diarrhea can be caused by infectious agents (enterotoxigenic *E. coli*, *Campylobacter*, *Shigella* and *Salmonella*), toxin ingestion, medications (broad spectrum antibiotics, metoclopramide, quinidine etc), ischemia and other conditions. Rota virus is a very common cause of diarrhea in children which causes inhibition of $\text{Na}^+ \text{K}^+$ ATPase through structural damage to mucosa. Increased activity of cyclic AMP and GMP (cholera, *Staphylococcus*, *Salmonella*) also causes diarrhea by increasing salt and water in stool. Besides, prostaglandins and Ca^{2+} also stimulate this process.

Antidiarrhoeal Therapy

Dehydration is the most common cause of death in case of diarrhea. So correction of fluid depletion, shock and acidosis are of central importance to all forms of acute diarrhea. Treatment should always be directed according to the underlying cause as most diarrhoea is self limiting. The treatment of diarrhea therefore, consists of correction of dehydration by oral rehydration therapy, maintenance of adequate nutrition and drug therapy which can be either specific against the microbials or non-specific antidiarrhoeal agents.

Oral Rehydration Therapy (ORT): It is the cornerstone of management of diarrhea. It is most advantageous when the fluid loss is mild (5-7%) and moderate (7-10%). The ORS

solution proposed by W.H.O. is most suited for cholera cases especially in children. Ideally the percentage of the constituents of ORS should vary for children, adult, cholera and non cholera cases.

Oral rehydration solution

Sodium chloride	-	3.5 g
Potassium chloride	-	1.5 g
Sodium citrate	-	2.9 g
Glucose	-	20 g
Water	-	1 litre

Na⁺ constitutes 90 mmol, Cl⁻ 80 mmol, citrate 30 mmol and glucose constitutes 110 mmol. Maximum absorption occurs with a slightly hypotonic solution with glucose concentration being in range of 80-140 mmol. Glucose concentration should always be greater than sodium concentration and solution should be isotonic to plasma. ORS should be taken at ½-1 hr interval and 5-7.5% body weight volume equivalent should be given in 2-4 hours duration. ORT does not stop diarrhea but restores the dehydrated state and fluid and electrolyte balance. Ringer lactate is recommended by W.H.O. especially in children.

Intravenous rehydration is recommended when fluid loss is >10% of body weight. The solution used is called Dhaka fluid consisting of:

Sodium chloride	-	85 mmol
Potassium chloride	-	13 mmol
Sodium bicarbonate	-	48 mmol
Water	-	1 litre

Super ORS : Improved ORS or super ORS have got additional antidiarrhoeal properties in addition to their curative property in comparison to the traditional ORS which have got property of only restoring the fluid loss. The glucose is replaced by starch based cereal powder which apart from facilitating the Na⁺ absorption, provides more calories as well as reduces the osmotic diarrhea induced by the glucose constituent in traditional ORS. Maltodextrins are also used in combination with glucose or alone. The low osmolarity also tends to reduce the stool output as both glucose and sodium concentrations are reduced.

Nutrition : Maintenance of nutrition is very important and the concept that greater intake of food causes more diarrhea should be completely abolished. Small but frequent meals apart from conventional foods like banana, mango, boiled rice, starch are helpful.

Drug therapy

Specific anti-microbials: Antimicrobials are useful in cases of severe infective diarrhea produced by microorganisms like *Shigella*, *Campylobacter*, *Salmonella*, *Y. enterocolitis* etc but very limited response is seen even in these cases. Rota virus diarrhea is generally self-limiting and does not need any drug therapy. Antimicrobials should be regularly used in cases of cholera (tetracyclines co-trimoxazole), *Campylobacter* (norfloxacin and other fluoroquinolones), *Clostridium difficile* (metronidazole, vancomycin), amoebiasis / giardiasis (metronidazole).

Non-specific anti-diarrhoeal agents: Non specific antidiarrhoeals constitutes mainly absorbants, antisecretory and antimotility agents.

a. Absorbants: Ispaghula, psyllium and methylcellulose are the most commonly used absorbants. They absorb water and increase the stool bulk. They increase stool viscosity and promote perception that there is decreased stool fluidity. They also bind enterotoxins, bacteria and foreign body. Cholestyramine is an anion-exchange resin which binds bile acid and enterotoxins. They also bind certain medications and vitamins so these should not be given within few hours of cholestyramine medication. Cholestyramine is used in bile-salt induced diarrhea and after resection of distal ileum. Absorbants are mainly used in irritable bowel syndrome and during ileostomy, colostomy diarrhea.

b. Anti-Secretory agents- Sulfasalazine, mesalazine, olsalazine, balsalazine, bismuth subsalicylate, atropine, octreotide etc.

Sulfasalazine and mesalazine is most effective in ulcerative colitis and other inflammatory bowel disease. These are made up of two compounds viz. 5-amino salicylic acid (5-ASA) and sulfapyridine joined together by an Azo bond. The Azo bond is split by colonic bacteria. Sulfapyridine acts as a carrier for 5-ASA and is responsible for the side effects. 5-ASA is the active agent responsible for local anti-inflammatory action. Dose required may be about 3-4 g/day. Major adverse effects include nausea, vomiting, headache, anaemia, male infertility and bone marrow suppression. These drugs are contraindicated in renal and hepatic failure. Coated mesalazine enhances gastric toxicity of glucocorticoids and hypoglycemic action of sulphonylureas.

Bismuth subsalicylate consists of 1:1 trivalent bismuth and salicylate suspended in magnesium aluminium silicate clay. It combines with the gastric HCl and forms bismuth oxychloride and salicylic acid. Salicylic acid is absorbed in stomach and small intestine. Bismuth has antisecretory (Traveller's diarrhea) anti-inflammatory and antimicrobial (*H. pylori*) effects. Bismuth sulphide if formed can blacken the stool and tongue.

Octreotide is used in diarrhea induced by hormones released by tumors in gastrointestinal tract and pancreas. Long acting preparation can be given as 20 mg intravenously once in a month.

Atropine is used in nervous- and drug-induced diarrhea.

c. Antimotility drugs: Codeine, diphenoxylate, atropine, difenoxin, loperamide, α_2 adrenergic agonist

Opioids mainly act through μ (motility) and δ (secretory) receptors present in the ENS, epithelial cells and muscles. Their function is to increase the tone of GIT.

Diphenoxylate, atropine, difenoxin are related to meperidine. Atropine is added to decrease the abusive liability. Common side effects include CNS depression and anticholinergic effects like dry mouth, flushing etc.

Loperamide is an opioid analogue with a weak anticholinergic property. It is quickly absorbed orally and is about 40 to 50 times more potent than morphine as an anti-motility agent. Available as capsule, solution and chewable forms, it has got poor CNS penetration and no abuse liability with longer duration of action. It increases the transit time, anal tone and has got antisecretory property. It also interacts with the calmodulin receptors. With a $t_{1/2}$ of 11 hours, it undergoes extensive hepatic metabolism. 4 mg should be given initially

followed by 2 mg after each subsequent stool with a maximum total dose of 16 mg/day. It is used as an adjunct with antimicrobials for traveller's diarrhea or as a monotherapy. It is contraindicated in children less than 2 years. Overdose may result in CNS depression (especially in children) and paralytic ileus. If improvement in diarrhea is not seen even after 48 hours of drug administration then loperamide should be discontinued. Caution should be taken while using in patients with inflammatory disease of colon.

α_2 -adrenergic agonists stimulate the absorption of water, inhibit secretion of fluid and electrolyte and increases the transit time. They have got special role in diabetics with chronic diarrhea. Oral dose- Clonidine, 0.1 mg, twice daily.

Cannabinoid receptor agonists decrease gut motility by decreasing Ach release from enteric nerves. Certain calmodulin inhibitors which include chlorpromazine also have antisecretory property. Zaldaride maleate is a novel drug effective against traveller's diarrhea.

Drugs Used for Dissolution of Gall Stones

The commonest pathological condition of the biliary tract is the formation of cholesterol gall stones. Cholesterol (CH) is solubilised in bile by the combined effect of bile acids (mainly cholic, deoxycholic and chenodeoxycholic) and phospholipids (mainly lecithin) which together form molecular aggregates called mixed micelles that are capable of keeping cholesterol dissolved within them. Cholesterol therefore, can precipitate if the concentration of lecithin and bile acids is too low or the concentration of cholesterol is too high which then may coalesce into cholesterol gall stones. Thus, reversing of the above situations is the basis of treatment for cholesterol gall stones by chenodeoxycholic acid (chenodiol) and 7 β -epimer ursodeoxycholic acid (ursodiol) while drugs like methyl tert-butyl ether and glyceryl-1-monooctanoate (monooctanoin) can directly dissolve the cholesterol stones.

The cholesterol gall stones which are small (<5 mm), floating in a functional gall bladder are amenable to treatment with drugs which can cause their dissolution. As these stones are radioluscent, multiple and may not respond with complete dissolution even with 2 years of appropriate therapy. In addition the recurrent rate after discontinuation of therapy is sufficiently high and given that recurrent stones may only infrequently causes symptoms; an additional course of therapy may be reserved for symptomatic recurrences. However, pigment stones and calcified cholesterol stones are not affected by above treatment (Table 3).

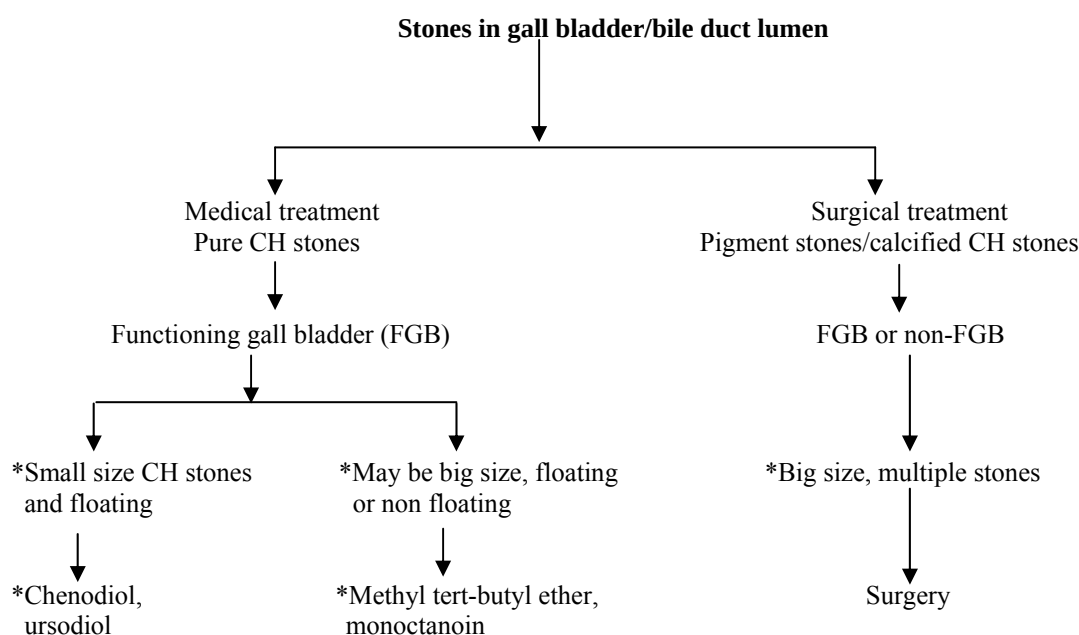
Oral therapy: Chenodiol, a primary bile acid (about 40% of the naturally occurring bile acids in man) and its 7 β -epimer, ursodiol are both effective in dissolving cholesterol stones. Chenodiol inhibits HMG-CoA reductase, a rate limiting enzyme converting bile salts into cholesterol, leading to an increase in bile salt excretion. Chenodiol is used in the dose of 10-15 mg/kg/day and dissolves the cholesterol gall stones over a period of 6 months to more than two years. It produces diarrhea in nearly 30 % of patients and increase serum aminotransferase level indicating slight liver damage. It should not therefore be given to patients of chronic liver or inflammatory bowel diseases or at risk of pregnancy.

Ursodiol reduces absorption of cholesterol from the gut, inhibits cholesterol synthesis by liver and expanding the bile acid pool. It does not suppress 7 α -hydroxylase, the rate limiting enzyme for bile acid synthesis and also appear to stabilize the canalicular membrane of hepatocytes. Ursodiol is more effective than chenodiol and is used at a lower dose of 7-10 mg/kg/day. Cholesterol stones are better dissolved and drug is better tolerated. As these two

drugs have different mechanism of action, attempt has been made to give them in combination in divided doses for better results with less individual drug toxicity.

The above agents can also be used in primary biliary cirrhosis and sclerosing cholangitis possibly acting by modifying the endogenous bile acid pool which are hydrophobic and damaging to hepatocyte to more friendly hydrophilic state.

Table 3 -Showing a schematic diagram of the treatment of gall bladder/bile duct lumen CH stones



Infusion therapy: Methyl tert-butyl ether and monoctanoin (glyceryl-1-monoctanoate) are infused directly into gall bladder and bile duct lumen to dissolve the cholesterol stones. They are reserved for selected patients who are not surgical candidates. Stones may be completely dissolved or sufficiently reduced in size to facilitate their subsequent removal.

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