Chapter 1

Drugs for Peptic Ulcer and Gastroesophageal Reflux Disease

CASE 1: PEPTIC ULCER DISEASE (PUD)

A 35-year-old adult male RX, complains of intermittent pain in the upper abdomen. Pain aggravated at night after taking large meal. He was fond of fried and spicy food. He is a chronic smoker of cigarettes and an occasional drinker of alcohol. His grandmother had died of peptic ulcer disease. Haemoglobin values were normal and there was absence of blood in stool and vomiting.

The patient took ranitidine over the counter (OTC) for 3 times daily for a week for the relief of pain. Later after consultation with the physician ranitidine was changed to famotidine.

Qa. What are the factors which lead to peptic ulcer formation?

Imbalance between gastroduodenal mucosal defence forces and the aggressive forces lead to the pathogenesis of peptic ulcer. Thus, ***increase in acid-pepsin secretion and decrease in mucosal resistance*** appears to be the basic cause for peptic ulceration.

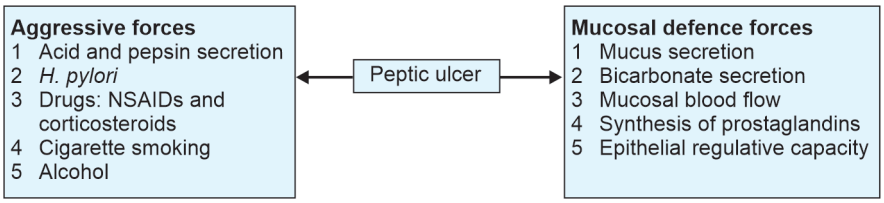

Fig. 1.1: Interplay of factors that contribute to pathogenesis of peptic ulcer

Qb. Explain the regulatory mechanisms for acid secretion from gastric parietal cells.

Neurologic, physical and hormonal stimuli release acetylcholine, gastrin and histamine which bind to their respective receptors on the basement membrane of the parietal cell. Through a cascade of events, increased intracellular calcium and raised cyclic AMP activates protein kinase A which stimulates the proton pump, the final common pathway which transports H^+ out in exchange for K^+. Chloride ions transported into the stomach lumen associate with H^+ ions to form hydrochloric acid (HCl).

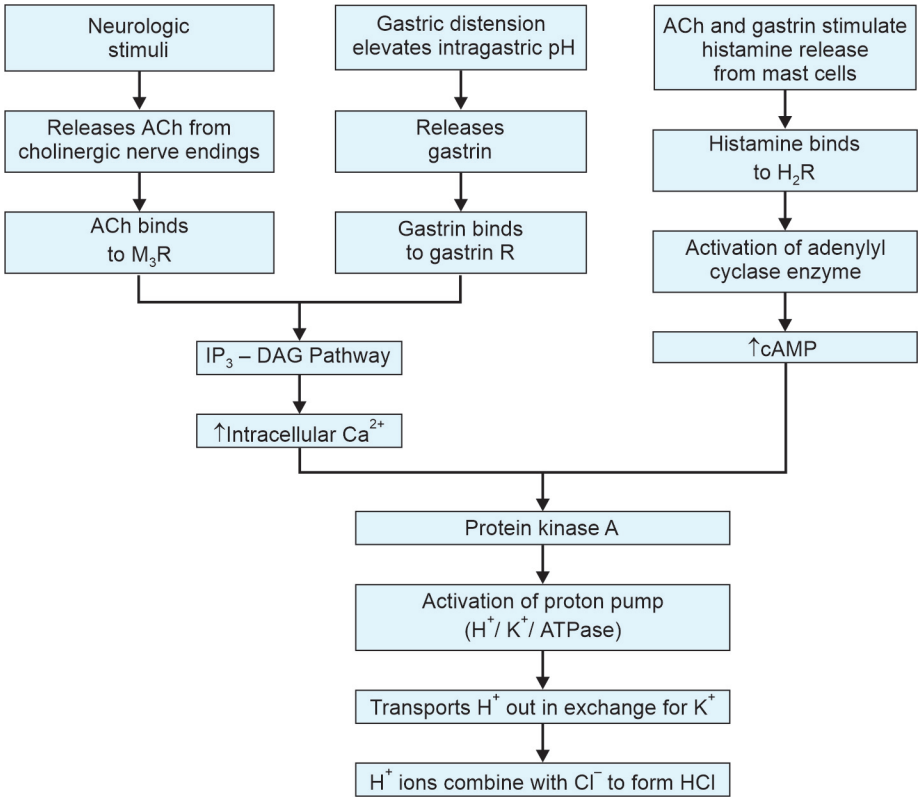

Fig. 1.2: Regulation of gastric acid secretion from the parietal cell

Qc. Which drugs are used for reducing acid secretion in peptic ulcer disease?

Drugs that reduce gastric acid secretion	
H2-receptor antagonists	Cimetidine, ranitidine, famotidine, nizatidine
Proton pump inhibitors	Omeprazole, rabeprazole, pantoprazole
Antimuscarinic agents	Pirenzepine, telenzepine
Prostaglandins	Misoprostol, enprostil, rioprostil

Qd. How is ranitidine or famotidine superior to cimetidine which is the prototypic H2- blocker in the treatment of dyspepsia?

Ranitidine and famotidine are superior to cimetidine in the following ways:

1. Both ranitidine and famotidine have greater potency and longer duration of action than cimetidine. This provides a longer duration of acid suppression.
2. Cimetidine crosses the blood–brain barrier and may induce mental confusion, headache and delirium. Ranitidine and famotidine have less penetration into the central nervous system, thereby producing less central adverse effects.
3. Cimetidine is antiandrogenic and increases prolactin levels, thereby leading to gynecomastia, galactorrhea, impotence and reduced sperm count in males. Hormonal side effects are minimal with ranitidine and famotidine.

4. Cimetidine inhibits CYP1A2, 2C9, 2D6 enzymes. Therefore, plasma levels of drugs metabolized by these enzymes may increase leading to toxicity. Ranitidine and famotidine have minimal or no action on hepatic CYP enzymes and decreased incidence of drug interactions.

Comparison of various H2-receptor antagonists			
Parameters	*Cimetidine*	*Ranitidine*	*Famotidine*
Bioavailability	80	50	40
Relative potency	1	5–10	32
Half-life (hrs)	1.5–2.3	1.6–2.4	2.5–4
Duration of action (hrs)	6	8	12
Inhibition of CYP450	1	0.1	0
Dose mg (bd)	400	150	20

Qe. Mr RX, wishes to take a H2-antagonist before he takes alcohol to avoid gastric irritation. He consults you. Which H2-antagonist will you ask him to take?

Mr RX was recommended famotidine and nizatidine because these have minimal effect on hepatic cytochrome P450 enzymes and hence do not affect the metabolism of alcohol unlike other H2-blockers which act as inhibitors of cytochrome P450 and thus inhibit the gastric first pass metabolism of ethanol increasing the concentration of alcohol in the blood producing undesirable effects.

Case Continued

Mr RX experienced pain more frequently and periods of remission decreased. Endoscopic examination revealed active duodenal ulcer. Mucosal biopsy suggested *H. pylori*. A case of duodenal ulcer associated with *H. pylori* was confirmed.

Qa. Mention the treatment regimen you would recommend for *H. pylori* eradication in peptic ulcer disease in case of RX.

Proton pump inhibitor (PPI) based standard tripple therapy (PPI-clarithromycin-amoxicillin) is an acceptable first line management strategy for RX because he has not received clarithromycin previously and has no known allergy to penicillin. Amoxicillin is usually preferred initially because it is associated with a little or no bacterial resistance, has fewer adverse effects, and leaves metronidazole as an option for second-line therapies.

If RX had a documented allergy to penicillin, metronidazole can be used instead of amoxicillin in the PPI-based three-drug regimen.

Bismuth-based quadruple therapy containing a bismuth salt, metronidazole, tetracycline, and either a PPI or H2-receptor antagonist has been frequently used as second line therapy.

Qb. What is the reasonable treatment period of eradication therapy for *H. pylori* infections with treatment regimens?

A 10–14-day-regimen is superior to shorter treatment regimens and is less likely to be associated with antimicrobial resistance. A treatment duration of less than 7 days is not recommended and is associated with unacceptable eradication rates.

Qc. Mention the benefits of combination therapy for treatment of *H. pylori* infection associated peptic ulcer disease.

The following benefits are achieved with combination therapy for H. pylori eradication:

1. Combination therapy increases the effectiveness of antimicrobial treatment regimen with improved eradication rates and reduced relapse rate of *H. pylori* infections.
2. There is lower risk of development of drug resistance with combination therapy compared to single antibiotic regimen.
3. The addition of proton pump inhibitor raises the gastric pH which enhances the efficacy of antimicrobials leading to faster ulcer healing effect and reduced risk of relapse.

CASE 2: ANTACIDS IN THE TREATMENT OF PEPTIC ULCER DISEASE

Mr JK, a 35-year-old male, after dining with friends in restaurant felt abdominal discomfort, nausea and belching. The patient comes to your clinic at midnight complaining of heartburn and abdominal discomfort. You want to relieve his pain immediately.

Qa. Which drugs would you recommend that produce immediate effect?

The patient may be prescribed antacids because antacids neutralize the acid which has already been secreted in the stomach and produces immediate relief of symptoms. All other drugs act by inhibiting acid secretion and so may not relieve symptoms for at least 45 min.

Systemic and non-systemic antacids can be recommended for the treatment of dyspepsia which are as follows:

Drugs that neutralize acid secretion	
Systemic antacids	Sodium bicarbonate, Sodium citrate
Non-systemic antacids	Magnesium hydroxide, magnesium trisilicate, aluminium hydroxide gel, magaldrate, calcium carbonate

Case Continued

Mr JK was prescribed an antacid preparation containing aluminium hydroxide and magnesium hydroxide.

Qa. Is it rational to combine aluminium hydroxide and magnesium hydroxide in antacid preparations? Explain.

Aluminium containing antacids relax gastric smooth muscle and delay gastric emptying and cause constipation as a side effect. Magnesium hydroxide, on the other hand, causes osmotic diarrhea. The combination of aluminium hydroxide and magnesium hydroxide counterbalances the effects of each other and preserves the normal bowel function. Also, magnesium hydroxide is rapidly acting and aluminium hydroxide is slow acting so the combination provides a relatively fast and sustained neutralizing capacity.

Qb. Explain why sodium bicarbonate is not the preferred antacid in peptic ulcer disease.

Sodium bicarbonate is not the preferred antacid in peptic ulcer disease due to the following reasons:

i. Sodium bicarbonate forms HCO_3^- ion which reacts with hydrochloric acid (HCl) to form CO_2 as one of the products and this leads to distension of the stomach, belching and increases the risk of rupture or perforation of peptic ulcer.

ii. HCO_3^- ion if absorbed systemically causes metabolic alkalosis.
iii. Sodium absorption may lead to retention of water which may aggravate edema and symptoms of heart failure.
iv. There is risk of acid rebound as the duration of action is short lasting.

CASE 3: PROTON PUMP INHIBITORS FOR THE TREATMENT OF PEPTIC ULCER

VK, a 56-year-old male patient, was diagnosed with duodenal ulcer associated with NSAIDs, he was receiving for pain relief of rheumatoid arthritis.

He was prescribed enteric coated capsule of omeprazole 40 mg daily in the morning 30 minutes before breakast, for three weeks.

Qa. The half-life of proton pump inhibitors is 1.5 hours but these drugs are generally given once daily instead of more frequent administration. Justify with reasons.

Proton pump inhibitors (PPIs) are selective and irreversible inhibitors of H^+-K^+-ATPase transport system which is the final common pathway responsible for acid secretion. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane and this takes at least 18–20 hours. Therefore, acid suppression continues for about 20–24 hours despite the short half-life of proton pump inhibitor and elimination of the drug from the body.

PPIs are prodrugs which freely diffuse into the parietal cell compartment and after conversion into sulfenamide, an active metabolite, gets trapped within the parietal cell, forms one or more covalent disulphide bond with the sulfhydryl group of H^+-K^+-ATPase leading to longer duration of acid suppression.

Qb. Explain why omeprazole, a PPI, is given as enteric coated granules in capsules or enteric coated tablet in the treatment of peptic ulcer.

Proton pump inhibitors are acid labile and degraded in the acidic pH of the gastric juice in the lumen of the stomach. The enteric coating of omeprazole protects it from the damaging effect of acidic gastric juice, thereby facilitates the drug to reach the intestine, wherein presence of alkaline pH enteric coating dissolves releasing the drug in the intestine and improving the absorption and bioavailability of the drug.

CASE 4: MISOPROSTOL FOR THE TREATMENT OF PEPTIC ULCER

A 72-year-old female LM, presented with acute peptic ulcer like symptoms. She is a known case of rheumatoid arthritis and there is history of frequent intake of high dose of aspirin for pain relief.

Qa. Given that the patient's history is suggestive of intake of high doses of aspirin and older age as an independent risk factor for NSAID induced ulcer, what drugs would you recommend for the prevention of gastric ulcer?

Both misoprostol and proton pump inhibitors (PPIs) have a similar efficacy in preventing gastric ulcer, but proton pump inhibitors (PPIs) are better tolerated than prostaglandin analogs. Therefore, proton pump inhibitors are preferred for the treatment of NSAID-induced ulcer.

Qb. How does aspirin induce gastric mucosal damage and ulcer formation?

Aspirin is an acidic drug and is largely unionized at acidic gastric pH and is absorbed from the stomach. The unionized form of acidic drug crosses the membrane of gastric

mucosal cell and is converted into the ionized form within the cell (pH 7.0). The ionized form of drug is trapped within the gastric mucosal cell causing injury to the mucosa and ulcer formation.

Aspirin like agents inhibit cyclooxygenase enzyme which mediates the formation of prostaglandins, that play a protective role on the gastric mucosa by enhancing the mucosal blood flow and reducing the gastric acid secretion. This reduces mucosal blood flow and produces areas of focal ischaemia and tissue damage which would subsequently be the sites of erosions and ulcers.

Qc. How is misoprostol useful in peptic ulcer disease?

Misoprostol, PgE1 analog has the following gastroprotective actions:

i. Increases mucus and bicarbonate secretion
ii. Enhances mucosal blood flow
iii. Increases in mucosal repair and restoration following gastric mucosal injury
iv. Inhibits gastric acid secretion in two ways: Directly by inhibiting acid secretion at the parietal cells and indirectly by inhibiting histamine release at enterochromaffin like cells.

CASE 5: MEDICATIONS FOR GASTROESOPHAGEAL REFLUX DISEASE (GERD) DURING PREGNANCY

A pregnant lady, Mrs TN visits the antenatal clinic with complains of heartburn and acid reflux and wishes treatment.

Qa. Which medications are safe and effective for heartburn during pregnancy?

H2-blockers or antacids may be used as first line agents for reflux. The use of proton pump inhibitors are reserved for more severe cases.

Ranitidine is the best studied agent effective for treatment of heartburn in pregnancy. Aluminium phosphate used as antacid therapy has been reported to provide complete relief of moderate to severe heartburn. Safety of proton pump inhibitors is not established in pregnancy. Misoprostol, a prostaglandin analogue, stimulates uterine contractions increasing the risk of abortion and early termination of pregnancy and therefore contraindicated in pregnancy.

Qb. Which drugs are preferred for the treatment of gastroesophageal reflux disease (GERD) in a non-pregnant adult?

In non-pregnant adults, proton pump inhibitors (PPIs) are more effective than antacids and H2-blockers for GERD and are preferred drugs.

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