CHAPTER-I

PEPTIC ULCER DISEASE: A REVIEW
1. INTRODUCTION

1.01. What is Peptic Ulcer Disease

The term generally refers to spectrum of disorders that include gastric ulcer, pyloric channel ulcer, duodenal ulcer and post-operative ulcers at or near the site of surgical anastomosis. Peptic ulcer may be characterized physiologically as a consequence of the inability of the localized areas of the stomach and duodenum to withstand the digestive action of acid and gastric juice thereby exposing the underlying layers of the gut wall to the acid reduction and the proteolytic enzyme pepsin\(^1\). Generally in gastric ulcers, the output of hydrochloric acid is normal or low, but its corrosive effects presumably surpass the diminished resistance of the mucosa while in duodenal ulcers, the secretion of hydrochloric acid is excessive, two or four fold greater than normal, and its digestive capacity exceeds the apparently normal resistance of the duodenal mucosa\(^1,2\). The stomach defends itself from these digestive fluids, acid and pepsin, in several ways. One way is by producing mucous, a lubricant like coating that shields stomach tissues. Another way is by producing a chemical called bicarbonate. The chemical neutralizes and breaks down the digestive fluid into substances less harmful to stomach tissues. Finally, blood circulation to the stomach lining, cell renewal and cell repair also help protect the stomach. What causes peptic ulcer, is not well understood phenomenon and for many years the main medical treatment has been aimed at reducing acid production, based on the hope that neutralizing gastric acid will reduce the efficacy of pepsin, and so allow ulcer to heal. More recent studies have shown a relationship between a microaerophilic bacterium \textit{H. pylori}, which appears to lie beneath the mucus membrane of the stomach wall and peptic ulcer\(^3,4\).
1.02. Scope of the Review

Present article is a systemic review, compiled to bring forth, the current information on the various aspects of disease including its epidemiology, diagnosis and various ways of treatment etc. Given a comprehensive account, it is an outcome of the compilation of researches done by various workers in different areas of peptic ulcer, help has taken from a number of standard books. Recent journals and research and review papers with modern concept of the disease incorporated, greater emphasis on various ways of treatment especially on proton pump inhibitors has been given. It is a sincere effort done to present this article in a way providing an overview of the disease updating our knowledge.

1.1. HISTORICAL PERSPECTIVE

Looking back at history, peptic ulcer was generally unrecognized as a cause of symptoms/complications or death until the early 19th century. Despite sporadic case report beginning in late 18th century, peptic ulcer did not become widely appreciated until early 20th century. The first 6 decades saw the dominance of surgery in the treatment of peptic ulcer. With the introduction of acid suppressive drugs like H-2 blockers in 1970s, the treatment of disease was revolutionized. By nineteen eighties, the advent of Helicobacter pylori brought about dramatic twist and possibly the cure.

1.2. BACKGROUND RATIONALE

Peptic ulcer is one of the important medical problem of our time. It affects a large number of people who are otherwise relatively fit. Peptic ulcer is the most common disease of gastrointestinal tract and it is estimated that approximately 10-20% adult male population in western countries will experience this disease at some time in their lives. It produces considerable illness and pain, resulting in great economic loss to the patients and their communities. There are a number of problems in assessing the prevalence of
peptic ulcer. In particular, many ulcers are asymptomatic and the accurate diagnosis of duodenal ulcer by radiometric method is difficult. Despite these difficulties, a number of methods have been used to measure the prevalence of peptic ulcer in the community; such methods have included post-mortem studies, the use of the incidence of perforation as an index, the number of prescription for histamine receptor antagonists and more recently endoscopic survey. In U.K., a number of studies have indicated that prevalence of peptic ulcers in the population is of the order of 6-13%, for men and 2-5% for women between the age of 15 to 64. In United State, the incidences of peptic ulcers are approximately 10%. The proportion of duodenal to gastric ulcer is 4:1. Each year ulcers affect about 4 million people. About 6000 people die of ulcer related complications. More than 40 thousand people have surgery because of persistent symptoms or problem from ulcers.

1.3. CAUSES OF PEPTIC ULCER

Numerous factors blamed in the pathogenesis of the disease. Many of these factors may be acquired during life, although some of these may already be predetermined. Historically, stomach acid has been the most common factor blamed. No acid – No ulcer is an old axiom, which may be questionable in the present time. As a group, patient with duodenal ulcer have high acid secretion. Increased acid secretion causes changes in the wall of duodenum, setting the stage for invasion by Helicobacter pylori. For almost a century doctors believed life style factors such as stress and diet are the predisposing factors, including hyper-acidity thereby causing ulcers. While scientific evidence refute. Several life style factors continue to be suspected of playing a role. These include cigarettes, foods and beverages containing caffeine, alcohol and physical stress. Studies have indicated that cigarette smoking increases one's chances of getting an ulcer. Smoking slows the healing of existing ulcers and also contributes to ulcer recurrence. Coffee, tea, color and foods containing caffeine seem to stimulate acid secretion in the stomach, aggravating the pain.
of existing ulcer. Ulcers are also more common in people who have cirrhosis of
the liver, a disease often linked to heavy alcohol consumption\textsuperscript{10}. Although
emotional stress is no longer thought to be a cause of ulcers, people with ulcers
often report that emotional stress increases the ulcer pain. Physical stress,
however increases the risk of developing ulcer particularly in stomach. Non
steroidal anti inflammatory drugs (NSAIDs)\textsuperscript{11} make the stomach vulnerable to
the harmful effects of acid and pepsin. NSAIDs such as aspirin, ibuprofen,
naproxen sodium are present in many nonprescription medications used to treat
fever, headache and minor aches and pains. These NSAIDs interfere with the
stomach's ability to produce mucus and bicarbonates and affect blood flow to
stomach and cell repair. They can all cause the stomach's defense mechanism
to fail, resulting in an increased chance of developing stomach ulcers. In most
cases these ulcers disappear once the patient stops taking NSAIDs.

1.3.1. RELATION BETWEEN \textit{H. pylori} AND DISEASE

In early nineteen eighties Warren and Marshall published their findings
about organism known as \textit{H. pylori} and linked them to gastritis and peptic ulcer
disease. Until then, HP was considered to be an artifact of the stain when
stomach biopsies were looked at under the microscope. It is now believed that
ulcer results from a complex interplay of acid and chronic inflammation
induced by HP infection even though exact mechanism has not been elucidated.
\textit{H. pylori} is a spiral shaped bacterium found in the stomach. Scientists believe
this damage of stomach wall is presumably because of \textit{H. pylori} shape and
characteristics. The bacterium survives in the stomach because it produces the
enzyme urease. Urease generates substances that neutralize the stomach's acid,
enabling the bacteria to survive. Because of their shape and the way they move,
the bacteria can penetrate the stomach's protective mucous lining. Here they
produce substance that can injure protective mucous lining and make the
stomach cells more susceptible to the damaging effects of acid and pepsin.
There are also some evidence that *H. pylori* lessen the level of ascorbic acid in gastric juice\textsuperscript{12,13}.

### 1.4. PHYSIOLOGICAL MECHANISM OF ACID SECRETION

One of the features of the mammalian stomach, considered to be hallmark of gastric function, is the ability to secrete acid. As the hydrogen ions are secreted and intragastric pH decreases to less than 3.5, the conversion of the zymogen pepsinogen to active proteolytic pepsin enzyme is facilitated. Another, one of the major role of acid is to kill bacteria and microbes to ensure a stable intragastric environment. Nevertheless, when bacteria are present, acid and pepsin do initiate the digestive process, and under certain circumstances they may injure the gastroduodenal mucosa. Human stomach contains nearly 1 billion parietal (oxyntic) cells, which are located in the walls of the midsection of oxyntic glands, the secretory unit of gastric mucosa. Distinguishing character of parietal cells are abundant mitochondria and tubovesicular and canalicular system\textsuperscript{14,15}. Elucidating the cellular mechanism involved in the hydrogen ion generation and secretion remains a difficult task because of the complexity of the regulatory process involved. Three distinctly different pathways deliver chemical messengers that stimulate acid secretion. The neurocrine pathway delivers transmitters such as acetalcholine, which are released from post-ganglionic nerves in the stomach wall; the endocrine pathway delivers hormone such as gastrin; and paracrine pathway delivers tissue factors; such as histamine, which are released from local storage sites and which diffuse across the intercellular space to their local target cells. Studies of various parietal cells obtained from various species, responding to histamine and acetalcholine and specific antagonists have permitted the characterization of receptors of various stimulants of the acid that are presumed to be located on the basolateral membrane of the cells. Although parietal cells have receptors for gastrin, but their response to gastrin is greatly potentiated when H\textsubscript{2} receptors are activated concomitantly. This histamine both transmits
and facilitates the stimulation of acid secretion by gastrin. Once the agonist binds to a specific receptor, secondary messengers are activated that act as transducer of signal thereby enhancing the cell functions. Histamine, but not acetalcholine or gastrin, presumably stimulates the parietal cell functions by increasing cyclic AMP production which then activates specific cyclic AMP-dependent protein kinases. Cholinergic agent e.g. acetylcholine, and gastrin, in contrast to histamine, appear to stimulate the parietal cells by increasing the level of cytosolic calcium in parietal cells. Shown below is the schematic representation of the physiological mechanism as well as sites of action of various antisecretory agents (Fig. 1).

![Diagram of the physiological mechanism of gastric acid secretion](image)

**Fig. I: APPROACHES TO THE INHIBITION OF GASTRIC ACID SECRETION**
1.5. DIAGNOSIS OF PEPTIC ULCER DISEASE

Until early 1900s, the diagnosis was made on clinical grounds. By 1912, Friedenwald published the first case series of 1000 cases of peptic ulcer. He claimed he had exercised the greatest care to eliminate all cases in which there was the slightest doubt. However, he did not provide any diagnostic clue as to how he distinguished between his 500+ cases of duodenal ulcer from 400+ cases of gastric ulcer. By the year 1925, fractional test meal was being widely used for diagnosis. Barium contrast studies were also in vogue by 1925 overtaking the rigid gastroscope, which were awkward to use. By 1950s flexible endoscopies revolutionized the direct visualization of ulcer disease. *H. pylori* may be presumed to be present in any patient with duodenal ulcer on endoscopy. However, many experts recommend documentation by microscopic examination of biopsy or urease test.

1.6. TREATMENT OF PEPTIC ULCER DISEASE

Foundation of ulcer therapy was laid in ancient times, when powdered coral, seashell or chalk was used to treat dyspepsia long before it was realized that peptic ulcer was causing the pain. By late 18th and early 19th century as PUD was beginning to be appreciated, newer therapies emerged. These included changing of environment, various kinds of diets including mercury, silver, alkalies etc. Thereafter came an era when vomiting and blood letting, applying leaches to the abdomen practiced enthusiastically. This was followed by Leube who introduced the concept of resting the bowel in late 19th century, which included starving the patient for 7 days without food or water. Many of his patients died because of azotemia. Meulengracht's early feeding regimen replaced Leube's ill conceived treatment in early 20th century. Psychotherapy became popular in mid 20th century. With this background, the current segment will deal with various ways of treatment, which are currently in practice.
1.6.1. ANTACIDS

Stomach pH ranges from pH 1 when empty to 7 when food is present. In normal adults, about 22 mEq of acid is secreted per hour by about 1 billion parietal cells present in the gastric mucosa. Antacids are weak bases as they raise the gastric pH above 4 or even more result in reducing the proteolytic action of pepsin. They also help to reduce spasm and cause symptomatic relief to pain. Gastric antacids have been mainly classified mainly in two groups.

I- Systemic antacids (alkalotic agents)

II- Non-systemic antacids (Local antacids)

I- Systemic Antacids

They get easily absorbed in systemic circulation and therefore are capable of changing pH of the blood. They may cause systemic alkalosis. Such alkalosis is also enhanced by chloride loss (vomiting, diarrhoea) and by sodium ion absorption. Examples of antacids belonging to this category are sodium bicarbonate and sodium citrate.

II- Non-Systemic Antacids

They are usually insoluble in water and are poorly absorbed due to their cationic nature. Since they do not have direct effect upon the acid base equilibrium of the blood, systemic allkalosis does not result e.g. aluminum hydroxide gel, magnesium trisilicate.

Systemic antacids are used to combat acidosis while local antacids are used in the treatment of peptic ulcer and hyperacidity. Most of the antacids marketed now a days are in mixture form. Gelucil is a preparation containing aluminium hydroxide and magnesium trisilicate combination. Magaldrate is a chemical combination of aluminium hydroxide and magnesium hydroxide. Milk has also been regarded as weak antacid having additional protective
action. Recently antacids formulations have come up with dried milk plus calcium carbonate and magnesium salt\(^{18}\).

1.6.2. CYTOPROTECTIVE AGENTS

Unlike H-2 inhibitors and acid pump inhibitors, these agents do not inhibit the release of acids. They shield the stomach's mucus lining from the damage of acid. Cytoprotection takes place in two ways. Below pH 4 there occurs extensive polymerisation and cross linking thereby binding to ulcer craters. Also, they stimulate the formation of Prostaglandins. Sucralfate (Carafate\(^{\circ}\)) is a complex formed from sucrose octasulfate and polyaluminium hydrate \((C_{12}H_{6}O_{11}[SO_{3}^{-}Al_{2}(OH)_{5}]_{8}\). Though a lot of drawbacks are associated with these agents. They adsorb a number of drugs upon their surface and reduce bioavailability (e.g. of digetoxin, phenatoin etc.)\(^{19}\). Misoprostol (Cytotec\(^{\circ}\)) is a systemic prostaglandin, a substance naturally produced by the body, protects the stomach lining by increasing mucus and bicarbonate production and by enhancing blood flow to the stomach wall\(^{20}\).

1.6.3. ANTIMUSCURINIC AGENTS

Before the introduction of H-2 blockers, these were the only that could reduce the output of acid secretion. These agents cause approximately 30% inhibition of acid-secretion. But their use is limited now a days due to so many side effects including dry mouth, visual disturbances, cardiac arrhythmias, constipation, urinary retention, drowsiness etc. Pirenzepine, a selective muscarinic (M\(_{1}\)) receptor antagonist can inhibit the stimulated secretion of acid by 50 to 60%. Both Pirenzepine and more potent Telenzepine are acute, hydrophilic and penetrate the blood brain barrier hardly. Other muscarinic antagonists are Menthanthelium bromide, Mepenzolate bromide\(^{21}\).
1.6.4. H2-INHIBITORS

The development in 1970s of H2-antagonist provided an incontrovertible evidence for the importance of endogenous histamine in the physiological control of gastric secretion. Early representatives of this group like Burimamide (Black et al., 1972) and Cimetidine (ID$_{50}$ = 1.4 µmol/kg, the first compound released for the general use) retain the imidazole ring while this ring is replaced by furan in Ranitidine (ID$_{50}$ = 1.1 µmol/kg) or a thiazole ring in Nizatidine (having ID$_{50}$ = 1.3 and 2.1 µmol/kg respectively).
1.6.5. PROTON PUMP INHIBITORS

Proton pump inhibitors are the most efficacious anti-secretory agents so far, appear to show real advance in peptic ulcer therapy. Proton pump is an enzyme $H^+/K^+$ ATPase is localized in the specialized acid secreting parietal cells of the gastric mucosa and produce a transmembrane proton gradient in excess of $10^6$. In the resting stage the pump is localized on the intracellular membranous tubovesicular system. Upon stimulation (by various protein kinases), however, this network fuses to become part of an expanded canaliculus which connects with the extracellular space. These morphological changes are accompanied by an increase in oxygen consumption and acid secretion into the canaliculus. The enzyme basically exists in major conformations $E_1$ and $E_2$, where present, the ion binding sites at cytosolic and extracellular surfaces of tubovesicle membranes respectively. Exchange of ions between intra and extracellular sites takes place at the expense of ATP via enzyme in its two conformation$^{14}$. The reaction path of the pump operation is given below:
Fig. 2: Schematic Representation of Pump Operation in acid secretion

(I) COMPETITIVE INHIBITORS OF H⁺/K⁺ ATPase

Studies with purified H⁺/K⁺ ATPase have demonstrated that inhibition of this enzyme by these inhibitors occurs in a competitive manner with respect to K⁺ ions. Schering Plough Corporation reported a potent anti-secretory agent in 1980s, the imidazo (1, 2α) pyridine derivative (SCH 28080). The compound was 50 times less potent by oral route (ED₅₀ = 4.4 mg/kg) than the I.V. route (ED₅₀ = 0.04 mg/kg) against histamine stimulated acid secretion in the Heidenhain pouch dog (might be due to first pass metabolism). But unfortunately further work was discontinued on this due to toxicity problem. Another imidazopyridine analog (SCH 32651) was found to be less potent antisecretory agent as compared to SCH 28080²²,²³.

(II) NON-COMPETITIVE INHIBITORS

AB Hassle (Sweden) group of workers have discovered an extremely efficacious class of anti-secretory inhibitors, the benzimidazoles sulfoxide. This
led to the discovery of Picoprazole and Omeprazole. This work also helped to generate an understanding the way in which enzyme operate. Various salient features of this group were:

(i) The weak basicity of the compound ($pK_a \approx 4$) allowed them to accumulate in the acid space adjacent to the site of action (secretory canaliculus of the parietal cell).

(ii) Sulfoxides themselves are inactive but under the influence of acid, are converted to some active species.

(iii) The active species being thiophilic in nature and covalently binds to the thiol functions (Cysteinyl residues) forms disulfide bridges to the enzyme$^{24,25,26}$ thereby causing inactivation (Fig. 3).

Fig. 3: Mechanism of action of benzimidazoles
Omeprazole was the first therapeutically proven proton pump blocker and clearly emerged as significant advance in treating peptic ulcer disease. Patients poorly responsive to treatment with histamine H2-receptor antagonist respond well to Omeprazole27. In patients with peptic ulcers, Omeprazole as a single 20 mg daily dose provides more rapid and complete healing compared with ranitidine 150 mg twice daily. Pantoprazole is also an irreversible proton pump inhibitor which, at the therapeutic dose of 40 mg, effectively reduces gastric acid secretion. The drug has lower affinity than Omeprazole or Lansoprazole for hepatic cytochrome P450 and shows no clinically relevant pharmacokinetic or pharmacodynamic interactions at therapeutic doses with a wide range of drug substrates for this isoenzyme system28. Rabeprazole has 2-10 fold greater antisecretory activity than omeprazole in vitro. However, it dissociates more readily from H+/K+ ATPase than Omeprazole, resulting in a shorter duration of action. Inhibition of the proton pump by Rabeprazole is partially reversible29.

Lansoprazole

Omeprazole

Pentoprazole

Ufiprazole

Rabeprazole
1.7. BASIS OF WORK, 4,5-CIS-5-STYRYL-2-OXO-OXAZOLIDINE-4-CARBOXYLIC ACID AND ITS PROFILE

Among the various constituents of food, protein and their breakdown products have been reported to be the major stimulant for gastric acid secretion\(^{30,31}\). Several workers have reported that i.v. infusion of mixture of amino acids lead to the potentiation of gastric secretion\(^{32,33}\), while others have reported that amino acid induced gastric secretion is not affected by H-2 inhibitors\(^{34}\). On the other hand, intraduodenal administration of amino acids leads to inhibition of Peptone stimulated gastric secretion. L-cysteine was also found to be protective against reserpine and pylorous ligation induced ulcers\(^{35}\). L-serine and L-glutamine also show dose dependent inhibition of gastric acid release and permit back diffusion of acid, after protection against stress, indomethacin and ethanol induced mucosal lesion\(^{36,37}\). L-Glutamic acid inhibited aminoacids and leucine induced acid secretion respectively\(^{38,39}\). L-Tryptophane through potentiated acid secretion\(^{40}\), but also provided protection against stress and ischaemia induced ulcers by scavanging free radicals, increasing prostaglandin synthesis and microsal blood flow\(^{41}\). Studies on mechanism of aminoacid dependent acid release modulation have indicated that amino acids act via both gastric dependent and gastric independent pathway\(^{42,43}\). There have been reports that hyper acid secretion induced by infusion of amino acids is not blocked by H2-antagonist. Baak et al. have shown that Omeprazole, a known protein pump inhibitor attenuated intravenous amino acids induced gastric acid secretion.

4,5-Cis-5-styryl-2-oxo-oxazolidine-4-carboxylic acid

Recent studies, which were undertaken at CDRI to study the effect of N-acyl derivatives of various amino acids, have culminated in the identification of an oxazolidinone derivative 4,5-cis-5-styryl-2-oxo-oxazolidine-4-carboxylic acid having good proton pump inhibitory activity. This compound is as potent as Omeprazole in in vitro inhibition of H\(^+\)/K\(^+\) ATPase, and in various animal
models. Studies have also shown that inhibition of the enzyme by the compound occurs in a competitive manner and it binds to the high affinity luminal K+ site. In order to investigate its antiulcer activity, the compound was studied against following model as cold restraint, forced swimming, pyloric ligation and aspirin induced gastric ulcer and indomethacin induced duodenal ulcer in rats. In cold restrained ulcer (2 h) model ED_{50} mg/kg, p.o. of compound was 20.8±2.0. In forced swimming model the ED_{50} of 19.9±3.4. In pyloric ligation induced gastric ulcer model, the ED_{50} was 18±2.2. Free compound and Omeprazole showed a dose dependent decrease in total and free acidity but Omeprazole showed no effect on pepsin and mucin secretion and in higher dose showed an increase in mucin secretion. In aspirin induced gastric ulcer model the ED_{50} of compound was 13.5±2.1. To see the effect of compound on duodenal ulcer, the indomethacin induced duodenal ulcer model was used and the ED_{50} was 29.5±2.3. In gastric proton pump, it inhibited H^+/K^+ ATPase activity of gastric membrane vesicle IC_{50} = 8 μm, whereas of Omeprazole IC_{50} was 10 μM showing equivalent effects. In general pharmacological studies, the LD_{50} of compound >300 mg/kg i.p. in mice, whereas of Omeprazole it was >4 mg/kg p.o. in mice. It was devoid of anticholinergic, H_{2} receptor blocking or prostaglandin like activities but inhibits pentagastrin induced gastric secretion^{44}.

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\text{Fig. 4: 4,5-cis-5-styryl-oxo-oxazolidine-4-carboxylic acid}
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Further work on peptic ulcer, relates to this active molecule of CDRI and is subdivided in two parts:

(a) Synthesis of some analogs related to 4,5 cis-5-styryl-2-oxo-oxazalidinone-4-carboxycylic acid

(b) Pharmacokinetic studies on 4,5 cis-5-styryl-2-oxo-oxazalidinone-4-carboxycylic acid.

1. Metabolic studies of 4,5 cis-5-styryl-2-oxo-oxazolidine-4-carboxylic acid in rat.

2. Pharmacokinetic studies of the compound from its prodrug.

1.8. CONCLUSION

Though ulcer may cause discomfort, rarely are they life threatening. With proper knowledge of the cause and treatment, most people find relief. Our understanding of the cause of peptic ulcer disease has changed dramatically over the last couple of decades. *H. pylori* has very prominent role in pathogenesis, thus subject to reinfection. Eradication of *H. pylori* infection is a major medical advance that can permanently cure most peptic ulcer diseases. Besides availability of H₂-inhibitors, advent of proton pump inhibitors marked a new era in the treatment of acid peptic disorders. Though drugs intended to block gastrin receptors *e.g.* benzotRIPT, proglumid, ramabamide, have also been developed but are not yet sufficiently potent to be of clinical use. PPI are the potent inhibitors of acid secretion can abolish acid output stimulated by any secretagogue. Omeprazole being very first therapeutically proven proton pump inhibitor, its high efficacy support the old axiom no acid-no ulcer. But it too has a lot of side effects including visual disturbances and skin rashes *etc.* Despite the limitations, benzimidazoles are frequently used for treating ulcer related disorders. Efforts are in progress towards synthesizing some more efficient acid
inhibitory agent with lesser or no side effects. 4,5-cis-5-styryl-2-oxo-oxazolidine-4-carboxylic acid currently undergoing advanced stage of clinical trial.
1.9. REFERENCES


5. Dr Minocha (http://www.diagnosishealth.com/minocha.htm)


