

Drug Treatment of Peptic Ulcer Disease

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ABSTRACT

Peptic ulcer disease is a widely prevalent upper gastrointestinal disorder worldwide. Gastric hypersecretion is recognized as the prime underlying cause of this disease. Earlier approaches towards alleviation of this disease have primarily focussed on symptomatic treatment of gastric hypersecretion with anti-secretory agents. Histamine H_2 receptor antagonists represented the first successful mechanistic intervention with acid hypersecretion and the prototypic drug cimetidine earned the title of 'first blockbuster drug' due to its stupendous sales. Cimetidine, ranitidine and famotidine remained as first-line therapy for peptic ulcer disease for a very long time. H_2 receptor antagonists had some limitations such as, ineffective daytime acid control, development of tolerance during therapy and acid rebound. Identification of the proton pump, $H^+/K^+ -ATPase$, as final source of gastric acid secretion led to development of another novel class of antiseecretory agents, termed as proton pump inhibitors (PPIs). These agents gave more potent and reproducible acid suppression compared to the H_2 receptor antagonists and soon became first line drugs

for the purpose. The prototypic agent omeprazole was soon followed by several other equally effective drugs like pantoprazole, lansoprazole and rabeprazole and these have commanded the antisecretory drug market ever since. Cytoprotective agents such as organobismuth compounds have also been used to reinforce the protective mucosal barrier in the stomach and intestine. Studies relating to the etiology and pathogenesis of this disease suggest that a majority of duodenal (95%) and gastric ulcers (70%) are associated with *Helicobacter pylori* (*H. pylori*) infection. This has led to the advent of additional therapeutic approaches for eradication of the bacteria. The present multidrug therapeutic regimens (triple therapy, quadruple therapy, etc.) for the treatment of peptic ulcer disease thus, include varying combinations of antibiotics such as amoxicillin, clarithromycin, metronidazole, etc. with proton pump inhibitors (less commonly, H₂ blockers) with or without cytoprotective agents.

INTRODUCTION

Peptic ulcer disease represents a widely prevalent problem of the gastrointestinal tract with annual incidence ranging from 0.10% to 0.19% [1,2]. This disease is characterized by secondary development of mucosal damage in the gastric or duodenal epithelium as a result of pepsin and gastric acid secretion. The damaging effects of gastric acid and pepsin overpower the protective mechanisms of the gastrointestinal mucosa, such as mucus and bicarbonate secretion resulting in formation of ulcers. The most common occurrence of the ulcers is in the stomach (gastric ulcer; GU) and proximal duodenum (duodenal ulcer; DU) with lesser instances in the lower esophagus, jejunum or the distal duodenum. There is an element of global variation in the prevalence of ulcers in general population. In western countries, the incidence of duodenal ulcers is thrice that of gastric ulcers. However, in eastern countries like India, Japan, Sri Lanka, the Andes, etc., gastric ulcers are more common [3]. Annually, around 500,000 persons in the United States develop peptic ulcer disease.

The earlier approaches towards alleviation of this disease have primarily focussed on symptomatic treatment with anti-secretory agents, however, the discovery of the prime link between the ulcers and *Helicobacter pylori* (*H. pylori*) infection has led to the advent of current therapeutic approaches directed towards the eradication of this bacteria. Presently, the predominant causes of peptic ulcer disease are recognized as *H. pylori* infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs), accounting for 48% and 24% of the cases, respectively [4]. Hence, the current recommendations for the drug treatment of peptic ulcer disease rely upon three main approaches used alone or in combination. These include- (i) eradication of the *H. pylori* infection with antibiotics; (ii) blocking the release of H⁺ ions from the parietal cells through irreversible binding of proton-pump inhibitors (PPIs) to H⁺/K⁺ - ATPase and (iii) blocking the acid-secretory effect of histamine (HA) by histamine H₂-receptor antagonists. The anti-secretory approaches alone were effective in alleviating ulcer disease, but the disease recurrence rates were very high. Ever since the introduction of combination therapy of anti-secretory agents and antibiotics [5,6], the recurrence rate of ulcers has significantly reduced.

The eradication of *H. pylori* reduces the recurrence of peptic ulcer disease for duodenal ulcers from 67% to 6% and for gastric ulcers from 59% to 4%. In the recent times, there has been an overall decline of peptic ulcer disease worldwide, which may be attributed to *H. pylori* eradication therapy coupled with the introduction of effective acid suppressive medications. According to the guideline issued by the American College of Gastroenterology (ACG) (2009) for prevention of NSAID-related ulcer complications [7], all patients beginning long-term NSAID therapy should be tested for *H. pylori* and NSAIDs should be immediately discontinued if the patients have positive *H. pylori* test results. If discontinuation of NSAIDs is not clinically feasible, maintenance with PPIs is recommended to prevent recurrences even after eradication of *H. pylori*. Cost factor has an important role to play in the selection of anti-secretory agents in antiulcer therapy. The studies of prescribing patterns of gastric acid suppressant treatment in peptic ulcer disease suggest a more frequent use of histamine H₂-receptor antagonists in comparison to proton-pump inhibitors (PPIs) in eastern countries like Japan, India, Malaysia, etc. due to higher cost burden of the latter [8]. Due to this reason, unlike the western countries, where PPIs represent the major therapies used to inhibit the production of gastric acid, PPIs constitute a very small part of this market (about 5%) in the East. Besides the antibiotics and anti-secretory drugs, the present day antiulcer therapy additionally includes cytoprotective drugs that work by reinforcement of the protective mucosal barrier [9]. These include bismuth compounds and prostaglandin analogues (misoprostol). Cytoprotective drugs have been out-dated by more effective therapies but, these are still being widely used in some countries like India and Japan [10]. Hence, current peptic ulcer therapy in *H. pylori*-positive peptic ulcers consists of eradication of *H. pylori* with antibiotics and use of PPIs or H₂ receptor blockers for healing and preventing peptic ulcers with or without cytoprotective agents. Antacids may also be included in the drug regimen to neutralize existing stomach acid and thus, provide rapid pain relief, however, these provide only symptomatic relief, but don't heal the ulcers.

This chapter reviews the chemistry and pharmacology of the major classes of drugs currently recommended in peptic ulcer disease.

PHYSIOLOGY OF GASTRIC ACID SECRETION

The glandular parts of the stomach located in the antrum and fundic regions are responsible for secretion of the enzymes and gastric acid for digestion of food. The acid-secreting oxyntic cells or parietal cells in the fundic region are the main sites of gastric acid secretion. The regulation of the secretion of gastric acid is carried out by various hormones and neurotransmitters (Figure 1). The parietal cell secretion of acid is mediated by the primary modulator histamine (HA) which may be released when enterochromaffin-like (ECL) cells are stimulated by gastrin (released from G cells of the antrum) and acetylcholine (ACh) (released from enteric neurons). Stimulation of the vagus nerve is known to initiate the release of both gastrin and acetylcholine (ACh) from their respective sites. Acetylcholine can also directly stimulate parietal cells to increase acid secretion.

Gastrin is also capable of stimulating the proliferation of the parietal cells by a direct action. Acetyl choline, histamine and gastrin stimulate acid secretion by activating specific G-protein-coupled receptors on the basolateral membrane of the parietal cells. ACh and gastrin activate phospholipase C to catalyze the formation of diacylglycerol and inositol triphosphate from membrane bound phospholipids. The release of Ca^{2+} from intracellular stores and the subsequent increase in cytoplasmic calcium ions (Ca^{2+}) activates H^+/K^+ -ATPase enzyme system (gastric proton pump). The binding of HA to the H_2 -receptor activates adenylate cyclase, resulting in an increase in cyclic AMP, which activates the proton pump [11]. The proton pump is thus, the terminal stage in gastric acid secretion, which makes it an ideal target for developing irreversible inhibitors of acid secretion.

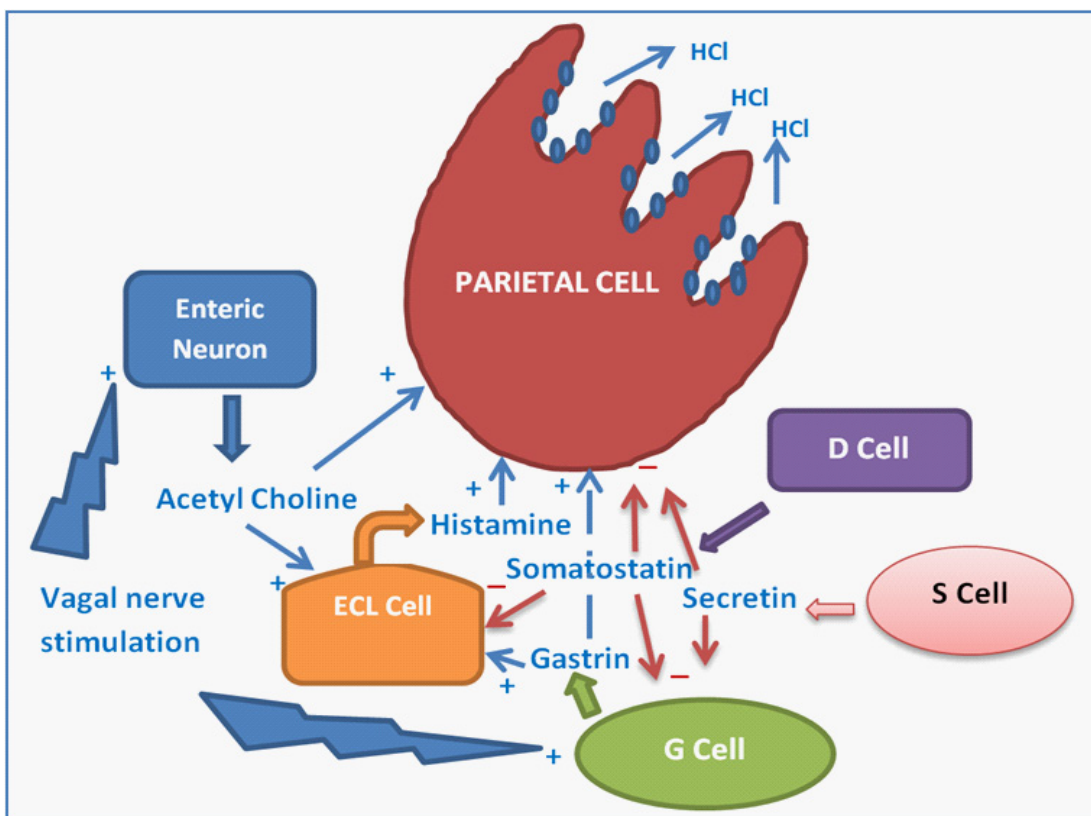


Figure. 1: Stimulation of acid secretion from parietal cells and its regulation.

Somatostatin, a peptide hormone released by the somatostatin secreting cells (D-cells) inhibits acid secretion by direct effects on the parietal cells (*via* a G-protein coupled receptor; by inhibition of adenylate cyclase, thus effectively antagonising the stimulatory effect of histamine), and also by inhibiting release of the positive regulators histamine and gastrin. The balance of activity of the different regulators changes as food is consumed and passes through different segments of the upper GI tract. Besides somatostatin, another peptide hormone secretin

(released by S-cells of the duodenum) also directly inhibits the secretion of gastric acid from the parietal cells. Secretin also has an indirect mechanism of acid regulation by inhibiting the release of gastrin in the pyloric antrum and by stimulating the release of somatostatin [12]. Another major function of secretin is to stimulate the release of aqueous bicarbonate solution from the pancreatic and bile duct epithelium. Other indirect regulators of gastric acid secretion include interleukins, cholecystokinin (CCK), neurotensin, vasoactive intestinal peptide, calcitonin gene-related peptide, oxyntomodulin, adrenaline, and gastric inhibitory polypeptide which can inhibit parietal cell acid secretion indirectly by the release of local somatostatin.

EXCESS SECRETION OF GASTRIC ACID

An imbalance between acid-secretory mechanisms and mucosal-protective factors results in peptic ulcers. Peptic ulcers are classified as Type I and Type II ulcers based on their underlying causes. Gastric acid hypersecretion is not a usual characteristic in Type I ulcers which result from impairment in mucosal protective factors. In comparison, gastric and duodenal ulcers are Type II ulcers which result from excess secretion of gastric acid or due to impaired negative feedback effects of acidification. Several causative factors of these ulcers are documented including *H. pylori* infection, drug therapy with non-steroidal anti-inflammatory drugs (NSAIDs) [13,14], environmental factors, and malignancy. Most patients with peptic ulcer disease are infected with *H. pylori* and only 10% of ulcers recur after eradicating the infection, possibly due to reinfection or due to the use of ulcerogenic drugs. Several classes of drugs have been used as antiulcer drugs including various anticholinergics, but the most successful classes of drugs have been those inhibiting gastric acid secretion and those eradicating *H. pylori* infection.

HISTAMINE H₂-RECEPTOR ANTAGONISTS

Histamine exerts a strong stimulant action on the gastric acid secretion from the parietal cells by acting on histamine H₂-receptors. The H₂-receptor antagonists were the first class of drugs to demonstrate an effective reduction in acid secretion. The discovery of H₂-receptor antagonists revolutionised the field of treatment of peptic ulcer as these were not only effective at healing ulcers but also kept them in remission when given as maintenance therapy [15-17]. Early studies indicated that these agents could heal peptic ulcers in 60% to 85% of patients within 4 to 8 weeks, compared to 20% to 40% healing rates in the placebo group. [18,19]. Currently, there are four US-FDA approved H₂-receptor antagonists in market: cimetidine, famotidine, nizatidine and ranitidine.

The advent of this class of drugs came in early 70s when Black *et al* [20] reported the discovery of thiourea derivative burimamide, the prototypic agent from this class, which inhibited acid secretion based on the antagonism of the histamine-2 receptors. Despite its higher potency over commercially available anti-secretory agents at that time (anticholinergics), its introduction into therapy was hampered by its poor bioavailability. Introduction of sulphur in the butyl chain and a methyl group in the imidazole ring afforded a ten times more potent and orally active analog

of bumiramide which was named as metiamide [21]. However, the drug had to be withdrawn from clinical trials due to incidence of agranulocytosis in some patients, an effect attributed to the presence of thiourea group in the structure. The first commercially available drug from this class of drugs was cimetidine (Figure 2) [22] which was introduced in 1976 (Tagamet® by GlaxoSmithKline) and subsequently approved by the US FDA in 1979. It was also effective in similar conditions like the Zollinger-Ellison syndrome, stress ulcers associated with burns, severe trauma, and brain and kidney damage. Cimetidine has been found to be curative in 70% to 92% of patients treated for duodenal ulcers and 70% to 100% effective in patients treated for gastric ulcers [23]. Cimetidine is also credited with the title of first blockbuster drug as it was marketed in over 100 countries and became the first drug ever to gross annual sales exceeding \$1 billion [24]. The discovery of cimetidine proved to be the turning point in antiulcer therapy paving way for several newer H₂-receptor antagonists with improved therapeutic profiles. Ranitidine (Zantac®) (Figure 2) was developed and introduced by Glaxo as a result of a rational drug-design process in 1981 [25]. The drug had the imidazole ring of cimetidine replaced with a furan ring containing a nitrogen-containing substituent. Its increased potency and far-improved tolerability compared to cimetidine coupled with a well-targeted marketing campaign established it as the world's most successful drug superseding cimetidine. Tiotidine [26] is a representative of the class of 2-guanidino-1-methylthiazole H₂-receptor antagonists (Figure 2) developed initially as an alternative to cimetidine. However, it could not be introduced into the market due to serious side effects. Some later studies have even contradicted its mechanism of action and it was suggested to possess H₂-receptor agonistic activity instead [27]. The replacement of the imidazole ring of cimetidine with a 2-guanidinothiazole ring yielded another successful drug, famotidine (Pepcid®) (Yamanouchi Pharmaceutical Company) in which cyanoguanidine group had additionally been replaced by a more hydrophilic sulfamoylamidine substituent (Figure 2). Famotidine is the most potent H₂ antagonist available for clinical use, being 20-50 times more potent than cimetidine and 6-10 times more potent than ranitidine [28]. Roxatidine, a representative of piperidinylmethyl-substituted phenyl ethers (Figure 2) is another drug from the class of specific and competitive histamine H₂ receptor antagonists [29] having a chemical structure quite different from the histamine molecule. Clinical studies have documented that the drug is equipotent to ranitidine [30]. Nizatidine (Axid®; Eli Lilly) (Figure 2) is an H₂ receptor antagonist equipotent to ranitidine possessing a thiazole heterocycle as replacement for the furan ring in ranitidine which was first marketed in 1987. Both nizatidine and roxatidine are commercially available, but they seem to offer no improvement over the other agents. Other H₂ receptor antagonists which have not got introduction to therapy include lupitidine [31] and oxmetidine [32] (Figure 2). Lafutidine (Figure 2) is a second generation histamine H₂ receptor antagonist [33] having a multipronged mechanism of action, marketed in Japan (Stogar® by UCB) and India (Lafaxid® by Zuventus Healthcare) to treat gastric ulcers, duodenal ulcers, stomach ulcers and for wound healing in acute gastritis. Besides H₂ antagonistic activity, the drug activates calcitonin gene-related peptide, with resultant stimulation of nitric oxide (NO) and regulation of gastric mucosal blood flow. It also increases

somatostatin levels and increases mucin production by the gastric mucosa. Lafutidine gives a prompt inhibition of gastric acid secretion not only at night but also during the daytime [34] which is a distinct advantage over all other first generation H₂ receptor antagonists. Further, recent studies have demonstrated a higher efficacy of this drug over lansoprazole, a proton pump inhibitor [35].

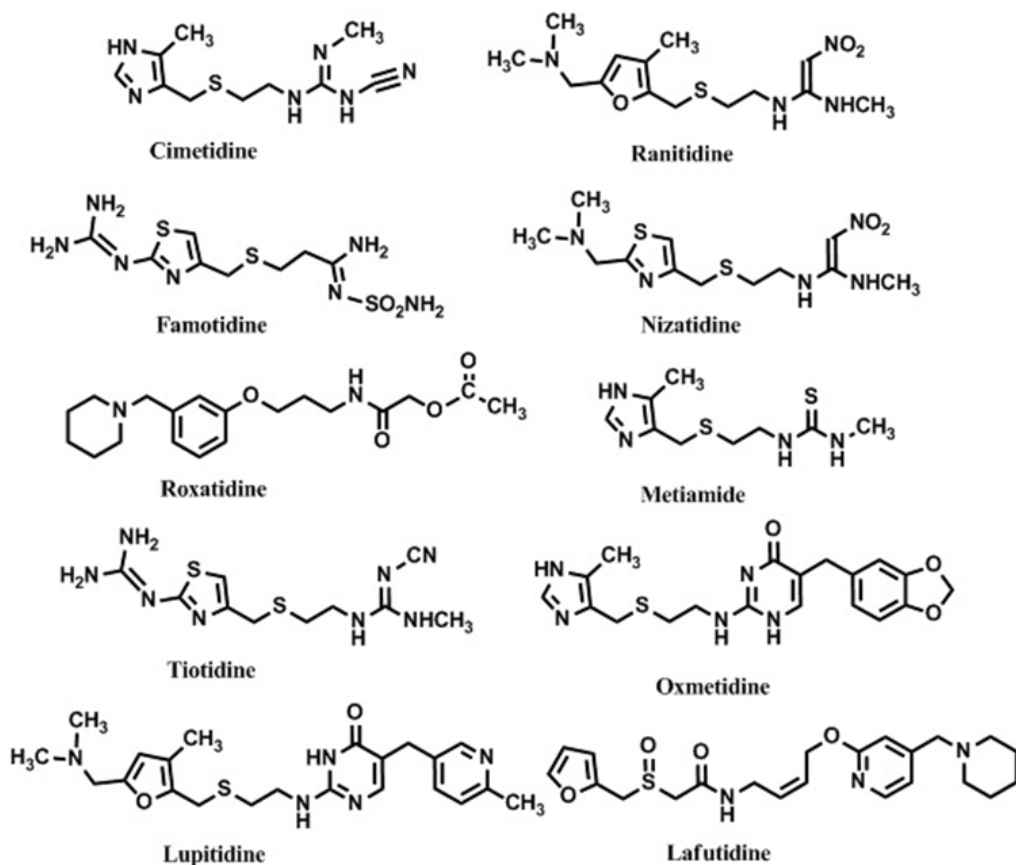
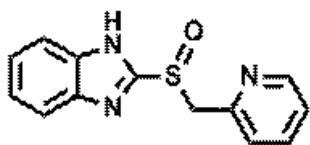


Figure 2: Representative histamine H₂-receptor antagonists.

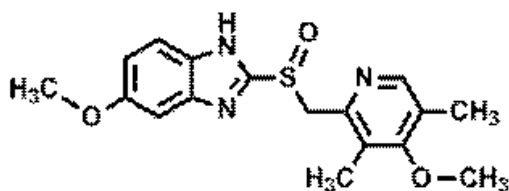
The H₂-antagonists became first-line therapy in peptic ulcer disease during the 1980s as these were representative of a systematic approach for the inhibition of acid secretion at the level of the parietal cells. Their addition to therapy with other classes of drugs like proton pump inhibitors is particularly recommended for improved nocturnal gastric acid control [36]. However, there were several reports of development of tolerance to H₂-antagonist therapy in some patients on long-term treatment [37,38] and acid rebound (elevated acid secretory response) after cessation of H₂ therapy [39]. Moreover, these drugs had little effect on the daytime acid control despite marked suppression of nocturnal acid output. This necessitated the exploration and development of newer and more effective anti-secretory agents.

PROTON PUMP INHIBITORS

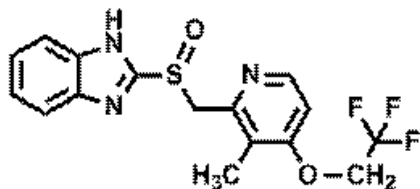
The electroneutral proton pump (H^+/K^+ -ATPase enzyme system (gastric proton pump) was discovered in the mid-70s [40,41] that worked against a concentration gradient to pump protons into the stomach lumen. Irreversible inhibitors of this system (proton pump inhibitors; PPIs) (Figure 3) were soon developed and these represented a significant advancement in the development of effective suppressors of gastric acid secretion. Unlike H_2 -receptor antagonists, which block a single stimulant of parietal cell acid production, PPIs inhibit the proton pump located on the luminal surface of gastric parietal cells, thus, exerting a direct suppressive effect on gastric acid that is more potent, of longer duration and free of tachyphylaxis [42]. In typical doses, these drugs can diminish the daily production of acid (basal and stimulated) by 80% to 95%. Proton pump inhibitors, in recent times, have become the first choice among medical practitioners for management and prophylaxis of peptic ulcers [43]. Peptic ulcer bleeding and re-bleeding after endoscopy is an additional cause of concern in antiulcer therapy. In the past two decades, proton-pump inhibitors (PPIs) have been extensively investigated as adjuvant therapy for acute bleeding ulcers [44]. The H_2 -antagonist therapy has not been found very useful in these cases but meta-analyses of several randomised trials have shown that PPIs effectively reduce re-bleeding compared with placebo or H_2 -receptor antagonists [45,46]. The results are however, questionable because, when studies with either a high or unclear risk of bias were removed, no difference was detected [47]. Panel recommendations for management of patients of upper gastrointestinal bleeding testify the use of intravenous high-dose PPIs after endoscopic therapy as the best-proven strategy [48]. Interestingly, PPIs are also reported to possess intrinsic antibacterial activity against *H. pylori* [49] besides producing a synergic pharmacokinetic interaction with the antibiotics [50,51]. The indiscriminate use of PPIs has, however, raised serious concerns as the administration of PPIs is associated with a significantly increased risk of infectious complications, especially of community-acquired or nosocomial pneumonia and *Clostridium difficile*-associated diarrhoea (CDAD) [52-54]. Large meta-analyses have confirmed these complications of PPI use [55].



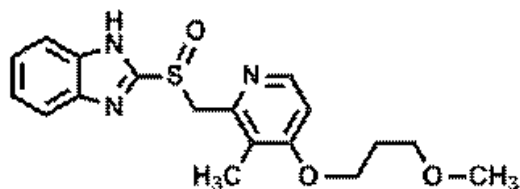
Timoprazole



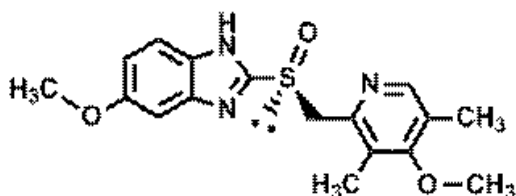
Omeprazole



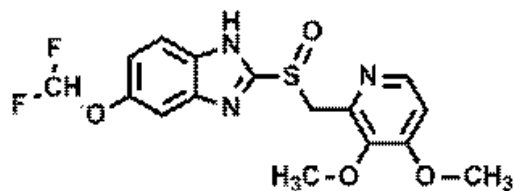
Lansoprazole



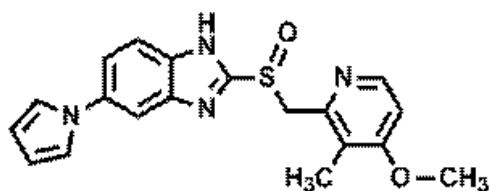
Rabeprazole



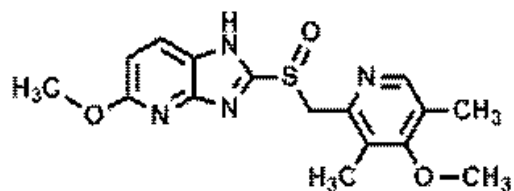
Esomeprazole



Pantoprazole



Ilaprazole



Tenatoprazole

Figure 3: Representative proton pump inhibitors.

The currently marketed PPIs are weakly basic benzimidazole based prodrugs (Figure 3) which don't have any effect on gastric acid secretion *per se*. These contain a benzimidazole system linked to a substituted pyridine ring through a methylsulfinyl linker. These are activated in the acid environment of the gastric glands (acidic secretory canaliculi) to their corresponding sulfenic acids/sulfenamides (Figure 4) which exist in equilibrium with each other and both of these covalently bond to -SH groups of the cysteine residues located on the luminal surface of the H⁺/K⁺-ATPase causing irreversible inactivation of the enzyme which accounts for their long-lasting inhibition of gastric acid secretion. Timoprazole was the first identified PPI [56] which was soon followed by its more potent analog picoprazole [57]. However, both these drugs had serious adverse reactions which led to further exploration of structure activity relationships in the compound series. Studies showed that the toxicities of these compounds could be effectively

separated from their proton pump inhibitory potency by selection of appropriate substituents in the benzimidazole and pyridine ring systems. Eventually, Omeprazole (Losec[®] by AstraZeneca) was the first drug to be marketed in 1988 for the treatment of ulcers caused by hypersecretion or diseases such as the Zollinger-Ellison syndrome. Losec[®] had become the largest selling prescription drug (\$5909 million) worldwide, by 1999 due to its higher efficacy over previously popular H₂-receptor antagonists. This period saw the entry of three more therapeutically useful benzimidazole based PPIs pantoprazole (Byk Gulden; 1997) [58,59], lansoprazole (Takeda-Abbott; 1995) [60,61], and rabeprazole (Eisai Co. Ltd; 1997) [62] into the anti-secretory market dominated by omeprazole and ranitidine. The four drugs omeprazole, lansoprazole, pantoprazole and rabeprazole (Figure 3) have similar mechanism of activation in parietal cells and show equal efficacy but studies show that pantoprazole has an improved bioavailability with insignificant effect on hepatic cytochrome P450 activity [58] but, rabeprazole has a more rapid onset of action than omeprazole [62]. Further, a number of studies have shown that rabeprazole possesses greater antibacterial activity against *H. pylori* compared to other PPIs [63,64]. Launched first in Japan in 1997, followed by Europe (1998) and the United States (1999), rabeprazole (Aciphex[®]; Eisai) is currently approved for treatment of various acid-related gastrointestinal diseases in more than 90 countries around the world. The product is co-promoted in the U.S. with Janssen Pharmaceuticals, Inc. With the patent for omeprazole expiring in 2001, AstraZeneca made an effort to retain its market by introducing its *S*-isomer (*S*-omeprazole; esomeprazole; Nexium[®]) claiming higher potency and improved pharmacokinetic profile [65] compared to omeprazole, lansoprazole, pantoprazole or rabeprazole [66,67]. Subsequent to its patent expiration in 2014, several other pharmaceutical companies have entered the market in 2015 with their generic versions of Nexium[®].

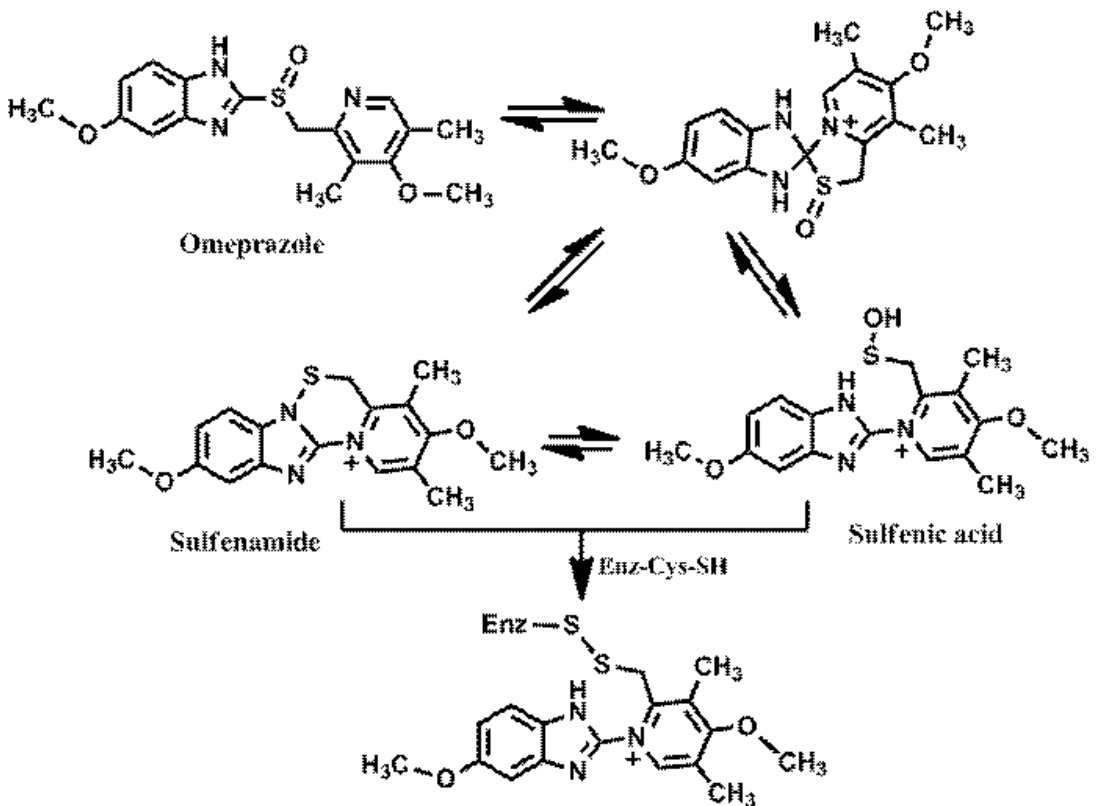


Figure 4: Acid catalyzed activation of proton pump inhibitors to pyridinium sulfenic acid or sulfenic acid represented by omeprazole.

S-Tenatoprazole (*S*-Benatoprazole; STU-Na) (Mitsubishi Pharma Corporation; NEGMA-Gild; Steba Laboratories) is a relatively newer proton pump inhibitor under clinical development with more potent acid inhibition and better nocturnal acid control than esomeprazole [68,69]. This drug is not a benzimidazole derivative but possesses an imidazopyridine system linked to the pyridyl ring through a sulfinylmethyl linker (Figure 3). It however, possesses the same mechanism of activation to sulfenamide or sulfenic acid in the parietal cells as other conventional PPIs. Although, its development for peptic ulcer has been recently discontinued, it is in Phase I studies for GERD. Ilaprazole is another benzimidazole based PPI in clinical development stage (Takeda Pharmaceuticals). The drug's anti-secretory activity and safety profile are superior to omeprazole [70].

ANTIBIOTICS

Studies show that majority of duodenal ulcers (95%) and a large percentage of gastric ulcers (70%) are associated with *Helicobacter pylori* (*H. pylori*) infection. Patients with documented ulcer disease and *H. pylori* infection, thus, need treatment for gastric secretion as well as *H. pylori* infection. Eradication of *H. pylori* has also been shown to prevent the recurrence of ulcers.

A combination of several antibiotics is required for eradication of *H. pylori*, in combination with proton-pump inhibitors or H₂ receptor blockers. Commonly used antibiotics are tetracycline, amoxicillin, metronidazole (Flagyl®), clarithromycin (Biaxin®), and levofloxacin (Levaquin®) (Figure 5). These are mostly employed in combination of at least two antibiotics because combination treatment is more efficacious and this also reduces the likelihood of development of resistance to the antibiotics.

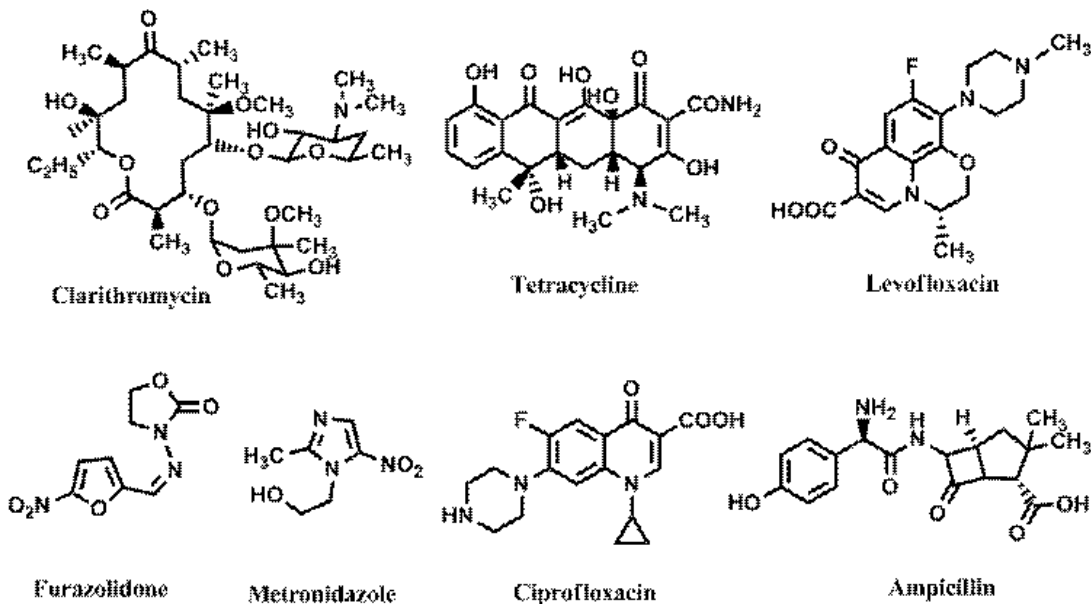


Figure 5: Antibiotics effective against *Helicobacter pylori* infection.

Amoxicillin (Figure 5) is a form of penicillin and it provides a highly cost effective antibiotic treatment. However, a significant percentage of population is allergic to beta lactam antibiotics (penicillins and cephalosporins). Clarithromycin (Biaxin®) is a macrolide antibiotic which is very effective against *H. pylori* infection. It is, however, the most expensive antibiotic used for this indication. Recent studies have shown a growing bacterial resistance to this drug which can further increase as more population uses the drug. Tetracycline is another effective antibiotic having its own unique side effects such as tooth discoloration in children. Pregnant women cannot take tetracycline. Fluoroquinolone antibiotics like ciprofloxacin and levofloxacin (Figure 5) have been less commonly employed in ulcer regimens. Initial combination regimens for *H. pylori* employed metronidazole (Flagyl®) (Figure 5) very frequently and it is a part of several combination regimens even now. However, bacterial resistance to this drug also seems to be growing. Other less frequently employed drugs include furazolidone (a nitrofurantoin antibacterial) (Figure 5) and rifabutin (a semi-synthetic derivative of rifamycin S).

As the prevalence of *H. pylori* antibiotic resistance increases worldwide, it is becoming a formidable challenge for the physicians to retain a balance between the effectiveness of antibiotic

regimens and growing resistance to these drugs [71]. Over the last 15 years, *H. pylori* resistance rates to metronidazole, clarithromycin and levofloxacin have increased several-fold [72] and this has had a major impact on the success of *Helicobacter pylori* eradication programs [73]. Last five year studies with antibiotic resistance have compared the resistance rates for various antibiotics [74]. These have been found to be as: metronidazole (47.22%) > clarithromycin (19.74%) > levofloxacin (18.94%) > amoxicillin (14.67%) > tetracycline (11.70%) > furazolidone (11.50%) > rifabutin (6.75%). Further, resistance shows a geographical variation with different regions showing differing rates of resistance to different antibiotics. Resistance of *H.pylori* to clarithromycin in UK is less than 5% whereas, in Spain and France, it is as high as 15-17%. The frequency of resistance to tetracycline, metronidazole and amoxicillin is higher in Africa, while clarithromycin and levofloxacin resistance is more common in North America and Asian countries, respectively [74]. Further, antibiotic therapy has its own set of problems, e.g., development of pseudomembranous colitis, a potentially severe infection caused by *Clostridium difficile*, an overgrowth of *Candida albicans*, resulting in vaginitis or gastrointestinal disturbances [75].

CYTOPROTECTIVE DRUGS

Another group of drugs has found its major application in protection against NSAIDs induced gastrointestinal mucosal injury (Figure 6). These drugs are directed towards reinforcement of the protective mucosal barrier in the stomach and the intestine. Prostaglandins are known to cause inhibition of adenylate cyclase activity in parietal cells, thus, exerting their anti-secretory effect on gastric acid. Further, these also stimulate the secretion of mucus and bicarbonate in adjacent superficial cells. Misoprostol (Cytotec®) (Figure 6) is a prostaglandin analogue which is a PGE₂ receptor agonist and it has been the most widely used, though, its application is limited by abdominal side-effects, especially at higher doses [76]. It is the only available oral prostaglandin in the United States and has been recommended for use with NSAID therapy to reduce the risk of gastric ulceration and bleeding. Combination products of misoprostol with NSAIDs (e.g., diclofenac) are also available. Organobismuth salts like colloidal bismuth subcitrate and bismuth subsalicylate (Pepto-Bismol®) (Figure 6) are also employed for their repairing actions on the gastro-duodenal mucosa [77] along with their antacid action. Such salts also possess some intrinsic anti-*H. pylori* activity and are combined with antibiotics for use in ulcer therapy [17]. Carbenoxolone (Figure 6) is a steroidal drug (glycyrrhetic acid derivative) used for the treatment of esophageal, peptic and oral ulcers and inflammation, however, the systemic administration of this drug is associated with electrolyte imbalance. Sucralfate (Carafate®) (Figure 6) is a complex salt of the sulfuric acid ester of sucrose (sucrose sulphate) and aluminium hydroxide which promotes mucosal repair resulting in healing of ulcers. Separation of aluminum in the acid environment of stomach forms a strongly anionic species that binds to positively charged proteins exuding from the ulcer forming a sticky paste. This binds to the ulcer surface and protects it from the harmful effects of acid, pepsin and bile. Sucralfate also utilizes its strong negative charge to inactivate pepsin and bile [78]. Additionally, this drug also works through suppression of *H. pylori* infection and reduction

of acid secretion [79]. Its use in peptic ulcer disease has diminished recently, but it is still the preferred agent for stress ulcer prevention [80].

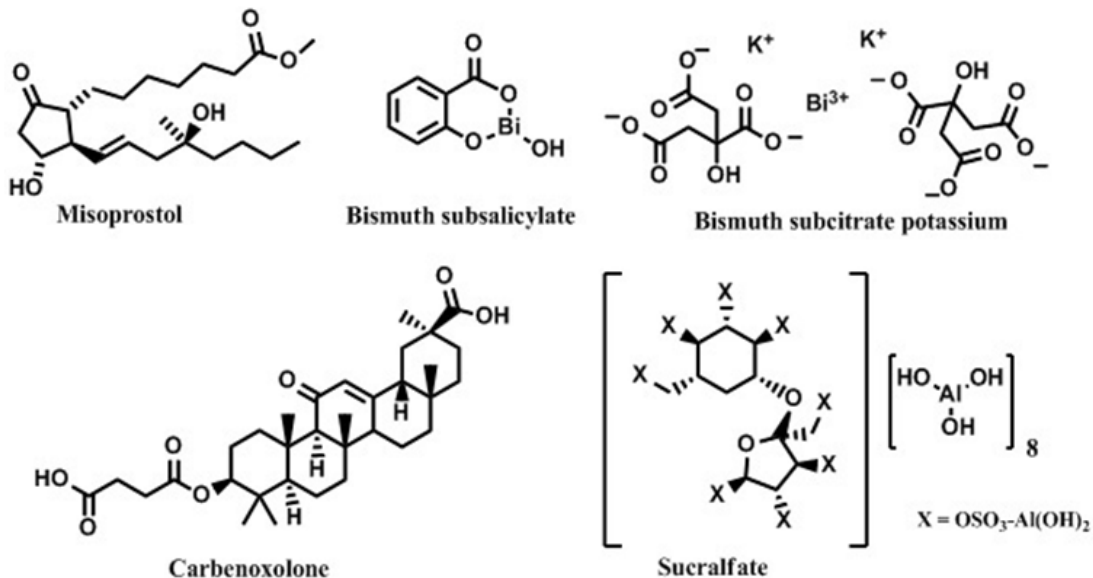


Figure 6: Cytoprotective agents in peptic ulcer therapy.

THERAPEUTIC REGIMENS

Treatment of peptic ulcers linked to *H. pylori* involves eradication therapy for *H. pylori* based on the combination of antibiotics and anti-secretory drugs [81]. Multiple studies and trials have been conducted employing varying combinations of antibiotics with H_2 receptor antagonists and good results have been obtained [82,83]. However, in recent times, the PPIs have invariably replaced H_2 receptor antagonists in such regimens due to their greater anti-secretory capacity, intrinsic antibacterial activity against *H. pylori* and their synergic pharmacokinetic interaction with the anti0biotics. Recently, a systematic review and meta-analysis was carried out with twenty published randomised studies to assess the *H. pylori* eradication efficacy of both groups of anti-secretory drugs on co-administration with the same two antibiotics [84]. Overall, a greater efficacy of PPIs versus H_2 receptor antagonists was evidenced (eradication rate of 74% vs 69%) from these meta analyses. However, there are a few studies showing equivalent efficacy of H_2 receptor antagonists to PPIs [85] with some studies even suggesting better results (lacking statistical significance) with the H_2 receptor antagonists compared to PPIs [86,87].

The first choice treatment for *H. pylori* positive ulcers is the triple therapy consisting of two antibiotics and one proton pump inhibitor for 7-14 days. In this regimen, the common medications for *H. pylori* eradication including antibiotics like clarithromycin, amoxicillin or metronidazole are combined with anti-secretory PPIs like rabeprazole, esomeprazole, lansoprazole, omeprazole or pantoprazole. All PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole)

are equivalent when given together with two antibiotics to cure the infection [88]. Usual combination is a proton pump inhibitor (omeprazole or esomeprazole) plus clarithromycin plus amoxicillin or metronidazole. H₂-receptor antagonists in triple therapy regimens are less effective than proton pump inhibitors. Quadruple therapy may also be started on failure of triple therapy, however, this can pose problems of compliance and increased side effects. It consists of bismuth, two antibiotics, and one proton pump inhibitor or H₂-blocker for 14 days. Usual H₂-blockers employed are nizatidine, famotidine, cimetidine or ranitidine. Commonly, a combination of a proton pump inhibitor with a bismuth compound (bismuth subsalicylate; Pepto-Bismol®) plus metronidazole plus tetracycline is employed. Prepackaged drug combinations are also available in the market, e.g., a combination of lansoprazole (a PPI), amoxicillin and clarithromycin (Hp-PAC®). Another combination regimen is sequential therapy in which, a combination of a PPI is given with an antibiotic like amoxicillin for the first five days followed by a combination of a PPI, clarithromycin and tinidazole for another five days. Several meta analyses have been performed to compare quadruple and triple therapy for primary treatment of *H. pylori* infection which suggest equivalent efficacy of both regimens [89,90] as first-line treatment. Currently, high dose PPI dual therapy is being investigated which involves the use of two PPIs (e.g., omeprazole 40 mg and lansoprazole 30 mg) along with an antibiotic (amoxicillin) for 14 days with encouraging results [91].

CONCLUSION

Drug therapy of peptic ulcers has evolved considerably in the recent times. Eradication of *Helicobacter pylori* infection has become an important part of the therapeutic regimens worldwide along with symptomatic cure with antisecretory drugs like PPIs (or H₂ receptor antagonists). This has considerably reduced the prevalence of *H. pylori* infections in developed western nations (about 10 per cent of population), though, in many developing countries, this rate is still as high as 80 per cent. Development of resistance of *H. pylori* to various antibiotics is an important cause of concern, and it has a global variation as well. This may partly be attributed to differing prescription patterns based on the drug availability and cost-effectiveness of the drug therapy. Easy availability of antibiotics without prescription in many countries leads to the misuse or overuse of antibiotics which not only leads to development of resistant strains of the bacteria but also hampers further investigations due to lack of proper documentation of antibiotic use. Caution also needs to be exercised with new therapeutic regimens. A balanced analysis of data concerning the success rate with different treatment regimens from different parts of the globe should be utilized in order to guide and manoeuvre the future therapy in this disease.

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