Review Article

PEPTIC ULCER AND ITS MANAGEMENT

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ABSTRACT

Ulceration of gastro-intestinal mucosa is caused by disruption of normal balance of corrosive effect of gastric acid and the protective effect of mucus on gastric epithelial cells. The major cause of ulcer is increased gastric secretions, which may be further aggravated by factors including NSAIDs, impaired production of somatostatins, Helicobacter pylori infection, by stress and dietary habits. Up to 80-90% of ulcers has been associated with H. pylori infection in the stomach. The parietal cells in the stomach secrete hydrochloric acid regulated by the protein H^+/K^+-ATPase also called proton pump. Acid secretion is also regulated by hormones such as gastrin, chemicals like acetylcholine and histamine. Acid neutralization was recognized as an effective treatment, however with the understanding of pathogenesis of peptic ulcer, treatment has become more effective. One approach for treating ulcer is to block the proton pump by using proton pump inhibitors like omeprazole, lansoprazole. In another approach, blocking of regulatory molecules that stimulate acid secretion like acetylcholine, histamine and gastrin either with anticholinergics or H_2 receptor antagonist such as ranitidine, famotidine is effective. H.pylori infection can be eradicated using amoxycillin, clarithromycin, metronidazole or tetracycline. Combination therapy helps in complete eradication of peptic ulcer; one of the combinations, approved by USFDA is omeprazole with clarithromycin. Gastro retentive dosage forms may prove beneficial as they exhibit a prolonged gastric residence time and act locally and systemically.

Key Words: Peptic Ulcer ,Management

INTRODUCTION

Mankind has lived with peptic ulcers since ancient times. Approximately 5-10% of general population will develop peptic ulcer during their lifetime, incidence of ulcer is common in men then in women[1,5]. Ulcer is a crater like lesion in a membrane; ulcers that develop in the region of gastro-intestinal tract (GIT) exposed to gastric acid are called peptic ulcers. Ulcers mainly occur either in stomach (98-99%) or in the duodenum in ratio of 4:1[6]. Ulceration of GIT mucosa is caused by disruption of normal balance of corrosive effect of gastric juice and the protective effect of mucus on gastric epithelial cells. Acid neutralization was recognized as effective treatment for more than 12 centuries ago but with the understanding of pathogenesis of peptic ulcer treatment has become more effective. In 1983, Warren and Marshall in Australia noticed the presence of curved bacilli in gastric biopsy specimen obtained from patient with active chronic gastritis and named it as Helicobacter pylori (earlier known as Campylobacter pylori)[1,4,7,8]. This discovery has further improved peptic ulcer treatment which includes combination antimicrobial agents with agents that effectively block acid secretion. This article discusses the various aspects of peptic ulcer and its management. The anatomy and physiology of stomach along with the regulation of acid secretion in order to understand the basics of peptic ulcer followed by drugs used in treatment has been discussed. A short review of delivery systems to optimize peptic ulcer therapy is also discussed.

Table 1: FDA-Approved Treatment Options [7]

1. Omeprazole 40 mg QD + Clarithromycin 500 mg TID x 2 wks, then omeprazole 20 mg QD x 2 wks
2. Ranitidine bismuth citrate (RBC) 400 mg BID + Clarithromycin 500 mg TID x 2 wks, then RBC 400 mg BID x 2 wks
3. Bismuth subsalicylate (Pepto Bismol®) 525 mg QID + Metronidazole 250 mg QID + tetracycline 500 mg QID x 2 wks + H_2 receptor antagonist therapy as directed x 4 wks
4. Lansoprazole 30 mg BID + Amoxycillin 1 g BID + Clarithromycin 500 mg TID x 10 days
5. Lansoprazole 30 mg TID + Amoxycillin 1 g TID x 2 wks
6. Ranitidine bismuth citrate 400 mg BID + Clarithromycin 500 mg BID x 2 wks, then RBC 400 mg BID x 2 wks
7. Omeprazole 20 mg BID + Clarithromycin 500 mg BID + Amoxycillin 1 g BID x 10 days
8. Lansoprazole 30 mg BID + Clarithromycin 500 mg BID + Amoxycillin 1 g BID x 10 days

Table 2: Generally prescribed therapy for H. pylori related ulcer[2]

1. Clarithromycin 500 TDS / Amoxycillin 750 BD + Omeprazole 40 OD
2. Amoxycillin 500 TDS / Tetracycline 500 QID + Metronidazole 400 QID / Tinidazole 500 BD + Bismuth 120 QID.
3. Amoxycillin 750 TDS + Metronidazole 500 TDS + Ranitidine 300 OD.

One week regimen

1. Amoxycillin 500 TDS/ Clarithromycin 250 BD +Tinidazole 500 BD/ Metronidazole 500 TDS + Omeprazole 20 BD.
2. Amoxycillin 500 TDS + Clarithromycin 250 BD + Omeprazole 20 BD

Anti Helicobacter pylori Kits (one kit to be taken daily in 2 doses)

1. HP-KIT, HELIBACT. OMXITIN: Omeprazole 20 mg 2 cap + Amoxycillin 750 mg 2 tab + Tinidazole 500mg 2 tab.
2. PYLOMOX: Lansoprazole 15 mg 2 cap + Amoxycillin 750 mg 2 tab + Tinidazole 500mg 2 tab.
3. LANSI KIT: Lansoprazole 30 mg 1 cap + Amoxycillin 750 mg 1 tab + Tinidazole 500mg 1 tab. (One kit twice a day).
4. PYLO KIT, HELIGO: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 caps + Tinidazole 500mg 2 tab.
5. LANPRO AC: Lansoprazole 30 mg 2 cap + Clarithromycin 250 mg 2 tab + Amoxycillin 750 mg 2 tabs.

Table 3: Adverse Drug Effect of Commonly Used Drugs in Ulcer Therapy

Name of Drug	Common	Rare
Omeprazole	Diarrhoea	Photosensitivity
Lansoprazole	Headache	Angioedema
Pantaprazole	Nausea	Alopecia
Rabeprazole	Constipation	Paraesthesia
Cimetidine	Dizziness	Headache
Raniditine	Fatigue	Liver dysfuction
Famotidine	Rash	Blood disorder
Sucralfate	Constipation	Nausea, Skin rashes
Misoprostol	Diarrhoea, Menstrual disorders	Dry mouth
Bismuth Chelate	Darkened tongue	Nausea

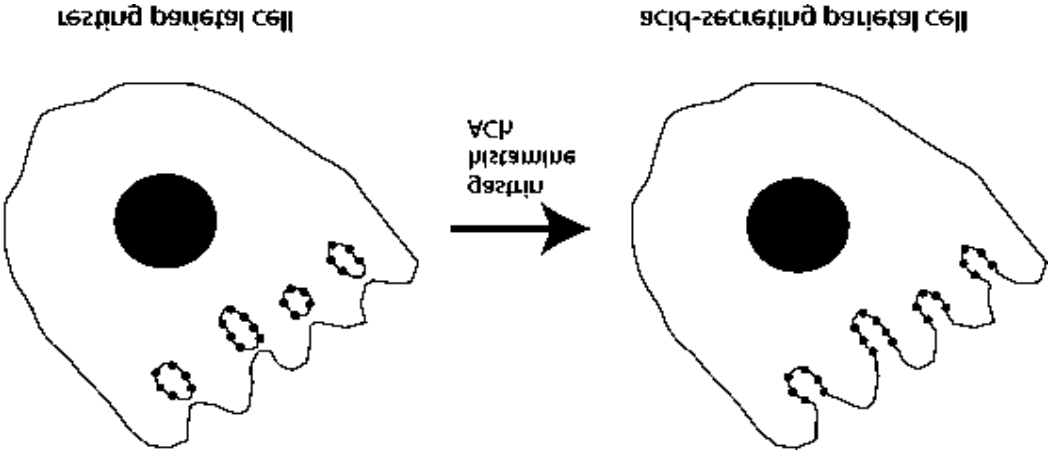

Figure 1(a)

Figure 1: a) Activation of parietal cells
1. b) Cephalic phase in acid secretion.

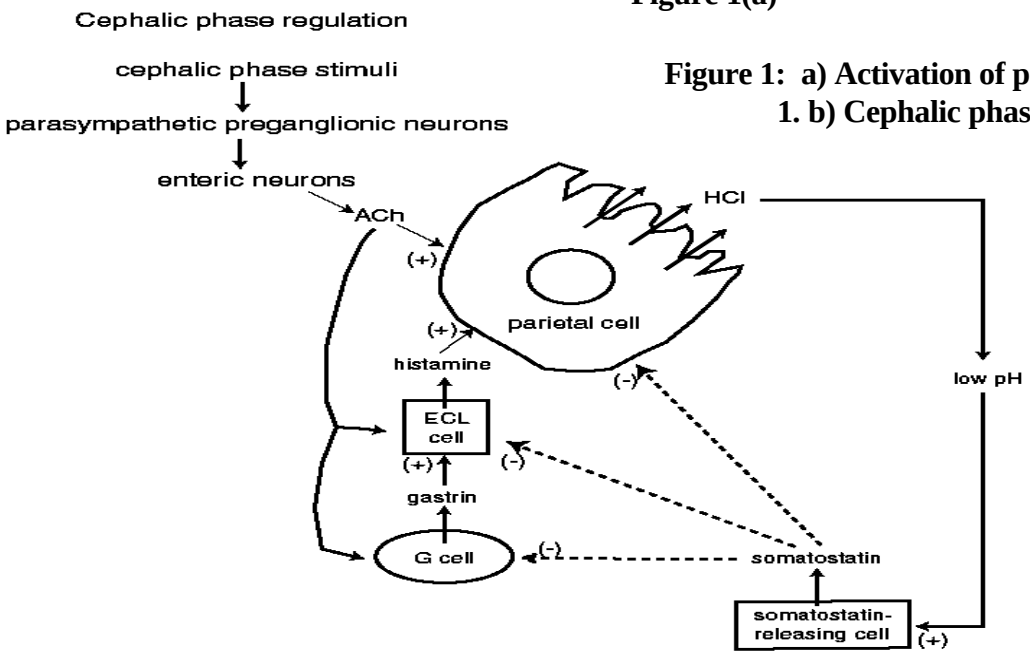

Figure 1(b)

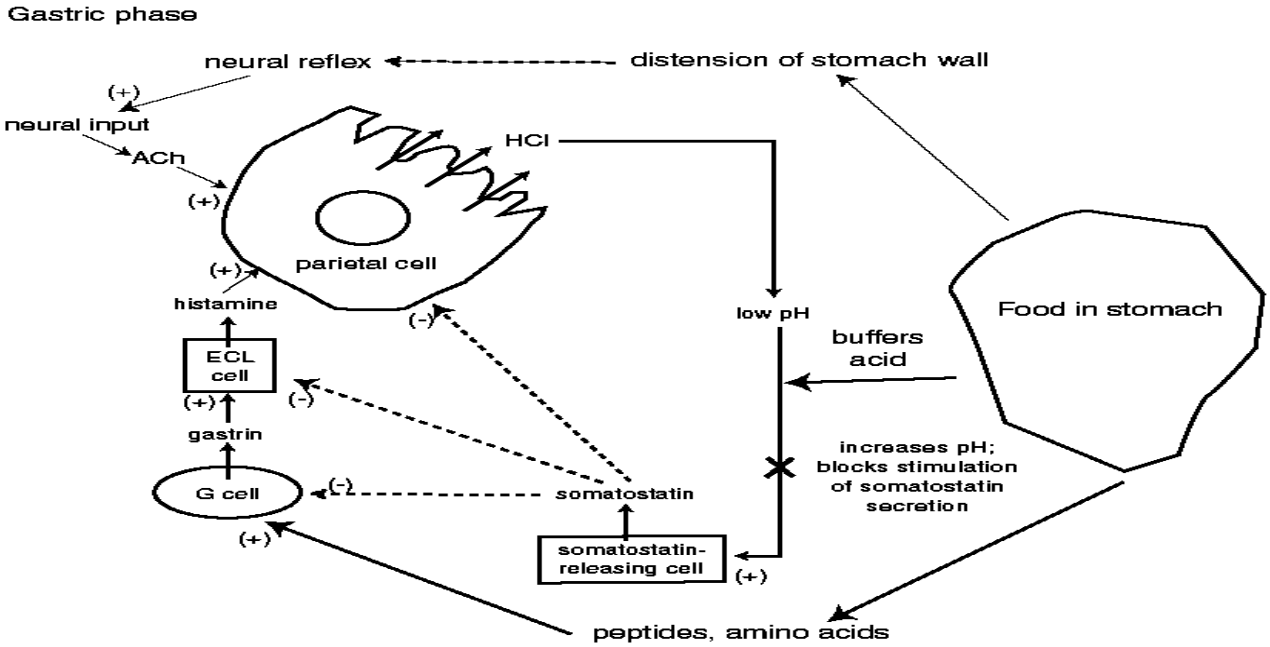

Figure. 2 (a)

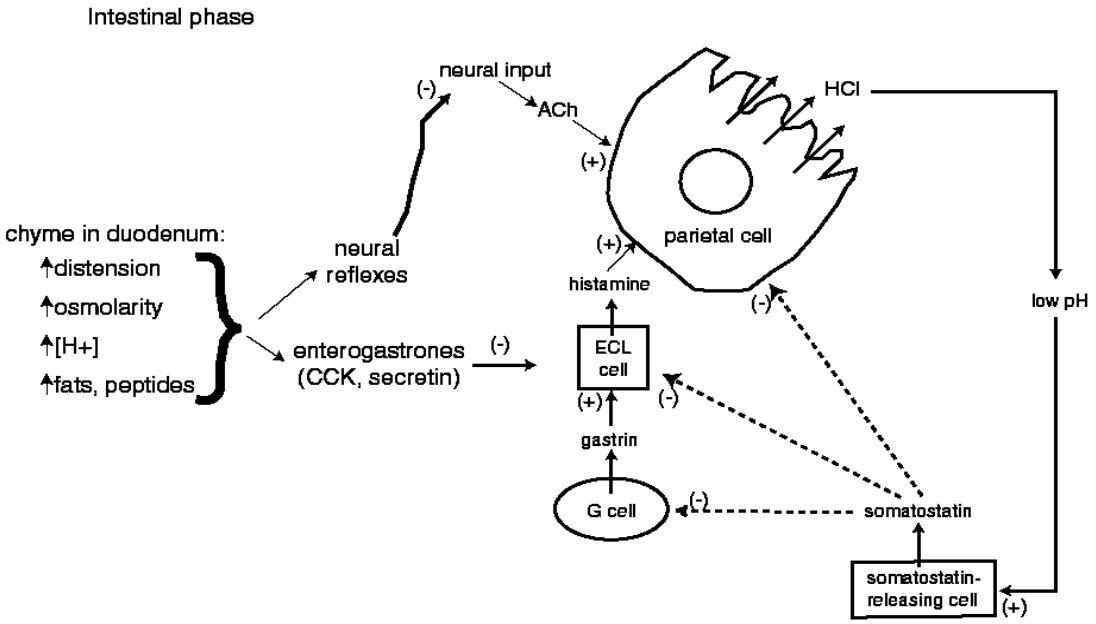

Figure. 2 (b)

Figure 2: (a) Gastric phase in acid secretion
2. (b) Intestinal phase in acid secretion.

Anatomy and Physiology of Stomach

There are four main regions in the stomach – **Cardia** surrounds superior opening of the stomach. The round portion superior to and to the left of cardia is **fundus**. Inferior to fundus is the large central portion of stomach called **body**. The region of the stomach that connects duodenum is the **pylorus**. It has two parts, the pyloric antrum that connects to the body of stomach and the pyloric canal, which leads into the duodenum. When stomach is empty, the mucosa lies in large folds called rugae. The pylorus communicates with the duodenum of the small intestine via a sphincter called pyloric sphincter. Stomach wall is composed of four basic layers; mucosa, a column of secretory cells called gastric glands which contain three types of exocrine gland cells that secrete their product into the stomach lumen, mucus neck cell which secrete mucus, Chief (zymogenic cell) which secrete pepsinogen and gastric lipase, parietal cell which produce hydrochloric acid and intrinsic factor. The secretions of mucus, Chief and parietal cells form gastric juice, which totals 2000-3000 ml/ day. In addition, gastric glands include a type of enteroendocrine cell, the G-cell which is located mainly in the pyloric antrum and which secretes the hormone gastrin into the blood stream. Gastric secretion is a complex continuous process controlled by multiple central and peripheral factors[2]. Parietal cells secrete H^+ ions. There are two pathways, which activate the process of gastric secretion viz., AMP dependent pathway and calcium dependent pathway. The $H^+ K^+$-ATPase pump, which is activated by both the pathways, generates largest ion gradient known in vertebrates.

Regulation of Acid Secretion

Parietal cells in the stomach secrete roughly two liters of acid a day in the form of hydrochloric acid. Acid in the stomach functions to kill bacteria and to aid digestion by solubilizing food, as it is important to establish the optimal pH (1.8-3.5) for the function of the digestive enzyme pepsin. A key protein for acid secretion is the H^+/K^+-ATPase (or proton pump). This protein, which is expressed on the apical membrane of parietal cells, uses the energy derived from ATP hydrolysis to pump hydrogen ions into the lumen in exchange for potassium ions. Stimulation of acid secretion involves the translocation of H^+/K^+-ATPases to the apical membrane of the parietal cell. When the cell is resting (not stimulated), H^+/K^+-ATPases are located in vesicles inside the cell. When the cell is stimulated, these vesicles fuse with the plasma membrane, thereby increasing the surface area of the plasma membrane and the number of proton pumps in the membrane. There are three regulatory molecules (Fig. 1) that stimulate acid secretion (acetylcholine, histamine, and gastrin) and one regulatory molecule that inhibit acid secretion (somatostatin). Acetylcholine, the neurotransmitter released by enteric neurons. Histamine the paracrine released from ECL (enterochromaffin-like) cells. Gastrin the hormone released by G cells, the endocrine cells that are located in the gastric epithelium. Somatostatin is also secreted by endocrine cells of the gastric epithelium; it can act as either a paracrine or a hormone.

Figure 1a show how the positive and negative regulators interact to stimulate acid secretion. Acetylcholine and histamine directly stimulate parietal cells to increase acid secretion. Gastrin stimulates acid secretion by stimulating histamine release from ECL cells. When the pH of the stomach gets too low, that stimulates somatostatin secretion. Somatostatin inhibits acid secretion by direct effects on parietal cells, and also by inhibiting release of the positive regulators histamine and gastrin. The different phases that regulate secretion of acid is discussed below:

Cephalic Phase

Cephalic phase is stimulated by the sight, smell, taste or thought of food. These stimuli, processed by the brain, activate enteric neurons via parasympathetic preganglionic neurons traveling in the vagus nerve. The vagus nerve in turn stimulate enteric neurons which stimulate acetylcholine as discussed earlier. This brings a cascade of reactions resulting in acid secretion. (Fig. 1b)

Gastric Phase

The primary factor during the gastric phase is that there is food in the stomach, which stimulates acid secretion. There are three different ways that this occurs. Food will stretch the walls of the stomach; this is sensed by mechanoreceptors, activating a neural reflex to stimulate acid secretion. Peptides and amino acids in food stimulate G cells to release gastrin. Food also acts as a buffer, raising the pH and thus removing the stimulus for somatostatin secretion. (Fig. 2a)

Intestinal Phase

Once chyme enters the duodenum, intestinal phase stimuli activate negative feedback mechanisms to reduce acid secretion and prevent the chyme from becoming too acidic. This occurs by neural reflexes and hormonal reflexes. En-

terogastrones are hormones that inhibit stomach processes (in this case, acid secretion). In addition to their other actions, CCK and secretin act as enterogastrones. (Fig. 2b)

The major cause of ulcer is increased gastric secretions, which further may be caused by environmental factors such as cigarette smoking, alcohol, spicy food etc, or drugs such as NSAIDS or by stress or by impaired production of somatostatins or may be due to bacterial infection such as Helicobacter pylori infection. Up to 80-90% of ulcers may be associated with Helicobacter pylori infection of stomach. This infection may lead to impaired production of somatostatins by D cell and in time decreased inhibition of gastrin with the resulting higher acid production as well as duodenal bicarbonate production.

Management of Peptic Ulcer[1,2]

The treatment of ulcer should be aimed at

1.Eradication of Helicobacter pylori infection

2.Reduction of stomach acid

3.Protection of stomach lining.

Eradication of Helicobacter pylori concurrently with H_2 blocker / proton pump inhibitor therapy of peptic ulcer have been associated with faster ulcer healing and lower relapse rate. Successful eradication relies upon patients adhering to their medication regimen. It is therefore important to educate patient about principles of eradication therapy. Drugs that suppress gastric acid production have proven their efficacy in variety of conditions in which acid plays a major role in injury to GIT mucosa. Some of the drugs with their mechanism were discussed below.

Proton Pump Inhibitors (PPI)

PPI's are prodrugs requiring activation in an acid environment. These agents enter the parietal cells and due to its basic nature PPI get accumulated in the acidic secretory canaliculi of parietal cell, where they are activated by a proton-catalyzed process that results in the formation of thiophilic sulfenamide. This activated form reacts by covalent binding with sulfhydryl group of cysteine from the extracellular domain of H^+K^+ ATPase. Binding to cystine 813 in particular is essential for acid inhibition. Various PPI's can be used such as Omeprazole (Prilosec), Lansoprazole (Prevacid), Rabeprazole (Aciphex) etc. Omeprazole is most preferable because in addition to inhibition of proton pump, it selectively inhibits gastric mucosal carbonic anhydrase, which may contribute to its acid suppressive properties and also inhibits activation of pepsin. It is interesting to note that plasma half-life of Omeprazole is 1-2 hours but they have the ability to inhibit acid production for more than 24 hours. PPI's is one of the combination drugs, which is used in the therapy of H.pylori infections. Most of the clinician treats all the patients with recurrent ulcers as well as those in whom H.pylori infection has been established with antimicrobial agents in combination with anti acid secretory drugs to eradicate H.pylori colonization.

H_2-receptor antagonist

H_2 receptor antagonist like cimetidine (Tagmet), ranitidine (Zantac), famotidine (Pepcid) and nizatidine (Axid). They reversively compete with histamine for binding to H_2 receptor on the basolateral membrane of parietal cells. These agents are effective in suppressing the nocturnal acid secretion and are most effective in duodenal ulcers, which can be healed with once daily dosing of H_2-receptor antagonist.

Prostaglandin analogs- Misoprostal

Prostaglandin's PGE_2 and PGI_2 are the major Pg synthesized by gastric mucosa; they inhibit acid secretion by binding to the EP_3 receptors on the parietal cells. Since NSAIDS inhibit PG formation, synthetic PG administered may be a rational approach to reduce NSAIDS related mucosal damage. Misoprostal is a synthetic PGE_1 given orally and approved by FDA for preventing mucosal injury caused by NSAIDS.

Sucralfate

In presence of acid induced damage, pepsin mediated hydrolysis of mucosal proteins contribute to mucosal erosion and ulceration. Process can be inhibited by sulfated polysaccharides such as sucralfate which is a sucrose sulfate-aluminum complex. Sucralfate in acidic environment undergoes extensive cross-linking and polymerization to produce a viscous, sticky gel that adheres strongly to ulcer craters for as long as 6 hours after a dose.

Antacids neutralize the excess of acid in stomach but cannot stop the production of acid.

Anticholinergic compounds

Pirenzine and telenzepine can reduce the basal acid production by 40-50% y antagonizing M_1 cholinergic receptors and gastrin receptors on the parietal cells (CCK_2 receptors).

Bismuth compounds are also frequently administered as one of the drug in the treatment of ulcer as they can bind to the base of ulcer, promotes mucin and bicarbonate production and above all has anti bacterial action.

Antibiotics

Antibiotics are prescribed along with other drugs for complete eradication of H.pylori infection. Amoxicillin, an aminopenicillin is highly effective against H.pylori by inhibiting the biosynthesis of dipeptidoglycans that is needed to provide strength and rigidity to bacterial cell wall. Macrolide antibiotics are another category of antibiotics, which are frequently prescribed such as clarithromycin. Agents that inhib-

its protein synthesis by binding reversibly to 50S ribosomal subunits of sensitive microorganism. Extended release form of clarithromycin, which is given, as a once daily 1gm dose should be administered with food, which improves its bioavailability. Tetracycline also has proven activity against H.pylori organisms. Metronidazole another antibacterial agent which is generally prescribed. Metronidazole is a prodrug, which requires activation of nitro group by susceptible organisms. Metronidazole involves radical mediated mechanism that target DNA biomolecules.

All of these drugs are prescribed in combination as either triple or quadruple therapy. The FDA approved treatment options have been summarized in Table 1. Further, a summary of the different prescribed therapy regimens alongwith the combination kits have been provided in table 2. Although these drugs are prescribed frequently they also posses some adverse drug reactions which are shown in table 3. There is a need for better therapy options to reduce the side effects observed in the triple and quadruple therapy.

OPTIMIZATION OF THERAPY:

Therapy for peptic ulcer can be optimized by means of various novel approaches. One of the novel drug delivery system which can be effectively used for treatment of peptic ulcer is Gastro retentive dosage forms (GRDF)[1-4]. GRDF is designed to exhibit a prolonged gastric residence time and have a potential for controlled drug delivery. Further, GRDF's can be retained in the stomach and assist in improving oral sustained delivery of drugs that have an absorption window in a particular region of gastro intestinal tract or topical delivery to the gastric mucosa, for example antibiotic administration for H.pylori eradication in the treatment of peptic ulcer disease would also be facilitated.

GRDF thus offers several advantages[1,4,5] over other oral controlled drug delivery system and can summarized as follows:

1.Site Specific drug delivery

Best approach for drugs for which local action is required, and delivers drug to site of action thus minimizing or eliminating side effects. Example, antibiotics for treating H.pylori infection including clarithromycin, amoxicillin, tetracycline etc.

2.Drugs that have poor bioavailability because their absorption is restricted to upper gastric intestinal tract can be delivered efficiently and thereby maximize their absorption and improving their absolute bioavailability, e.g. frusemide, riboflavin and prednisolone.

3.Floating systems prepared from anionic exchange resins that could also be used as a protective barrier against gastro esophageal reflux.

4.Floating drug delivery systems may result in complete removal of H.pylori in the fundal area of gastric mucosa due to bactericidal drug levels being reached in this area, might lead to better treatment of peptic ulcers.

APPROACHES FOR GRDF[1, 4,6]

Various approaches have been developed to increase retention of oral dosage form in the stomach including floating systems swelling and expanding systems, bioadhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices.

Basically three approaches were developed for formulating GRDF. They include

1. Incorporation of passage delaying food excipients, principally fatty acids to decrease gastric emptying rate.
2. Bioadhesive research based upon adhesive capacity of some polymer with glycoproteins.
3. Other approaches are to alter the formulations density by using either high or low-density pellets.

To achieve these approaches basically two systems have been widely used i.e. non-effervescent systems which includes Hydrodynamically balanced intra gastric delivery system, Intragastric Floating GIT drug delivery system, Inflatable gastrointestinal drug delivery system, Intragastric osmotically controlled drug delivery system and Bio (muco) adhesive gastrointestinal drug delivery system. Effervescent systems are prepared with swellable polymers such as hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose, carboxy methyl cellulose, chitosan etc., and effervescent component e.g. sodium bi carbonate, citric acid or tartaric acid or matrices containing chambers of liquid that liquefies at body temperatures. The effervescent systems after reaching stomach, carbon dioxide is liberated by the acidity of gastric content and is entrapped in jellified hydrocolloids, resulting in upward motion of the dosage form to float on the chyme.

So this can be novel approach, which can be used effectively for treatment of peptic ulcer, which not only provide patient compliance but also by use of this approach we can achieve local as well as systemic action there by rapid healing with lesser dose and side effects of drugs.

CONCLUSION

Ulcer heals in 4-8 weeks but may relapse unless H.pylori infection is treated successfully. Current research is based on identification of cause of H.pylori infection and effective means of its eradication. The treatment of ulcer should therefore be focused on eradication of H. pylori infection, reduction of stomach acid and protection of stomach lining. Gastro retentive dosage forms have the potential for use as controlled release drug delivery systems. GRDF has an additional advantage for drugs that are absorbed primarily in the upper

segment of GIT. They would provide the best result for drugs that act locally or those are absorbed primarily in the stomach. For many drugs that are absorbed mainly from proximal small intestine controlled release in stomach would result in improved bioavailability. So this can be a novel approach, which can be used effectively for stomach infections, which not only provides patient compliance but also may result in dose reduction and ultimately in reduction of side effects of drugs.

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