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AN OVERVIEW OF TREATMENT MODALITIES FOR PEPTIC ULCER

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ABSTRACT

Both duodenal and gastric ulcer disease are closely associated with Helicobacter pylori infection. An infected individual has an estimated lifetime risk of 10 -20% for the development of peptic ulcer disease, which is at least 3-4 fold higher than in non-infected subjects. Many drugs are been used as inhibitors of acid secretion and antacids are also effectively used. New potential drugs are also developed and introduced for acid related disease. Combination therapy like triple and quadruple therapy more effective for removal of Helicobacter pylori. Homeopathy and Ayurvedic therapy are also consider as treatment of ulcer. Role of surgery can be option for the bleeding ulcer or ant severe case.

KEYWORDS: Ranitidine, Famotidine, Clarithromycine, Misoprostol, Vonoprazan, Soraprazan, Revaprazan, Anti-helicobacter pylori Vaccine.

INTRODUCTION

Peptic ulcer disease (PUD), also known as a peptic ulcer or stomach ulcer, is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus.[1] An ulcer in the stomach is known as a gastric ulcer while that in the first part of the intestines is known as a duodenal ulcer.Complications may include bleeding, perforation, and blockage of the stomach. Bleeding occurs in as many as 15% of people.[2]

Common causes include the bacteria, Helicobacter pylori and non-steroidal anti-inflammatory drugs (NSAIDs).[1] Other less common causes include tobacco smoking, stress due to serious illness, Behcet disease, Zollinger-Ellison syndrome, Crohn disease and liver cirrhosis, among others.[3]

SIGNS AND SYMPTOMS

- Abdominal pain, classically epigastric strongly correlated to mealtimes. In case of duodenal ulcers the pain appears about three hours after taking a meal;
- Bloating and abdominal fullness
- Water brash (rush of saliva after an episode of regurgitation to dilute the acid in esophagus - although this is more associated with gastroesophageal reflux disease)
- Nausea, and copious vomiting;
- Loss of appetite and weight loss;
- Hematemesis (vomiting of blood); this can occur due to bleeding directly from a gastric ulcer, or from damage to the esophagus from severe/continuing vomiting.
- Melena (tarry, foul-smelling feces due to presence of oxidized iron from hemoglobin);
- Rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis, extreme, stabbing pain, and requires immediate surgery.[4]

ALREADY USED DRUGS

1. Gastric acid secretion inhibitors

I. H_2 Receptor Blocker

Cimetidine and **Famotidine** binds to an H_2-receptor located on the basolateral membrane of the gastric parietal cell, blocking histamine effects. This competitive inhibition results in reduced gastric acid secretion and a reduction in gastric volume and acidity.[5] [7]

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors found in gastric parietal cells. This results in decreased gastric acid secretion and gastric volume, and reduced hydrogen ion concentration.[6]

Cimetidine's side effects can include dizziness, and more rarely, headache. It is a known inhibitor of many isozymes of the cytochrome P450 enzyme system. (specifically CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4).[8]

II. Proton Pump Inhibitor

Omeprazole, Pantoprazole and Esoprazole are the proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, both drugs blocks the final step in acid production, thus reducing gastric acidity.[9,10] This effect is dose- related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus.[11]

III. Anticholinergic

Pirenzepine is a muscarinic receptor antagonist and binds to the muscarinic acetylcholine receptor. The muscarinic acetylcholine receptor mediates various cellular responses, including inhibition of adenylate cyclase, breakdown of phosphoinositides and modulation of potassium channels through the action of G proteins.[12]

IV. Prostaglandin Analogues

Misoprostol seems to inhibit gastric acid secretion by a direct action on the parietal cells through binding to the prostaglandin receptor. The activity of this receptor is mediated by G proteins which normally activate adenylate cyclase. The indirect inhibition of adenylate cyclase by Misoprostol may be dependent on GTP. Misoprostol is only indicated for use by people who are both taking NSAIDs and are at high risk for NSAID-induced ulcers, including the elderly and people with ulcer complications.[13]

2. Antacids

I. Systemic

Sodium bicarbonate is a systemic alkalizer, which increases plasma bicarbonate, buffers excess hydrogen ion concentration, and raises blood pH, thereby reversing the clinical manifestations of acidosis. Sodium bicarbonate acts as an antacid and reacts chemically to neutralize or buffer existing quantities of stomach acid but has no direct effect on its output. This action results in increased pH value of stomach contents, thus providing relief of hyperacidity symptoms.[14]

II. Non-Systemic

Aluminum hydroxide, Calcium carbonate, Magnesium hydroxide are a basic inorganic salts that acts by neutralizing hydrochloric acid in gastric secretions. Aluminum hydroxide is slowly solubilized in the stomach and reacts with hydrochloric acid to form aluminum chloride and water. It also inhibits the action of pepsin by increasing the pH and via

adsorption. Cytoprotective effects may occur through increases in bicarbonate ion (HCO_3^-) and prostaglandins.[15]

3. Ulcer Protectives

Sucralfate is a prescription medication used to treat peptic ulcers. The current clinical uses of sucralfate are limited. It is effective for the healing of duodenal ulcers, but it is not frequently used for this since more effective drugs (e.g. proton pump inhibitors) have been developed. Although the mechanism of sucralfate's ability to accelerate healing of duodenal ulcers remains to be fully defined, it is known that it exerts its effect through a local, rather than systemic, action.[16]

Sucralfate is a locally acting substance that in an acidic environment (pH < 4) reacts with hydrochloric acid in the stomach to form a cross-linking, viscous, paste-like material capable of acting as an acid buffer for as long as 6 to 8 hours after a single dose. It also attaches to proteins on the surface of ulcers, such as albumin and fibrinogen, to form stable insoluble complexes. These complexes serve as protective barriers at the ulcer surface, preventing further damage from acid, pepsin, and bile.[17]

Bismuth Subcyclate

Bismuth subsalicylate is used as an antacid.

Bismuth subsalicylate hydrolyzes in the gut to bismuth oxychloride and salicylic acid . By this mechanism it inhibit proliferation of H. pylori[18]

4. Anti-Helicobacter Drugs

(ANTIBIOTICS)

Antibiotics can cure most peptic ulcers caused by *H. pylori* or *H. pylori*-induced peptic ulcers. However, getting rid of the bacteria can be difficult. Amoxicillin acts by inhibiting the synthesis of bacterial cell walls.[19] Clarithromycin prevents bacteria from growing by interfering with their protein synthesis.[20] Metronidazole and Tinidazole inhibits nucleic acid synthesis by disrupting the DNA of microbial cells.[21,22] Tetracycline inhibits protein synthesis by blocking the attachment of charged aminoacyl-tRNA to the A site on the ribosome. Tetracycline binds to the 30S subunit of microbial ribosomes. Thus, it prevents introduction of new amino acids to the nascent peptide chain.[23]

NEW and POTENTIAL DRUGS IN MARKET

1. Vonoprazan

Vonoprazan (Takecab(®)) is an orally bioavailable potassium-competitive acid blocker (P-CAB) being developed by Takeda for the treatment and prevention of acid-related diseases. The drug is approved in Japan for the treatment of acid-related diseases.[24]

2. Soraprazan and Revaprazan

Soraprazan and revaprazan block H^+secretion much more quickly than classical PPIs (within a half-hour).[25] The development of soraprazan, however, was discontinued in 2007.[26]

3. Ilaprazole

Ilaprazole is a proton pump inhibitor (PPI) used in the treatment of dyspepsia, peptic ulcer disease (PUD) & gastroesophageal reflux disease (GERD).Ilaprazole is developed by IL-YANG Pharmaceutical (Korea), and is still under clinical trials with US FDA. It has launched in Korea and China for the treament of GU, DU, and GERD/EE.[27]

4. Dexlansoprazole

Dexlansoprazole permanently binds to the proton pump and blocks it, preventing the formation of gastric acid.[28]

5. Tenatoprazole

Tenatoprazole has an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors, and has a half-life about seven times longer than other PPIs.[29]

COMBINATION THERAPY FOR REMOVAL OF HELICOBACTER PYLORI (*Helicobacter pylori* eradication protocols)

Helicobacter pylori eradication protocols is a standard name for all treatment protocols for peptic ulcers and gastritis; the primary goal is not only temporary relief of symptoms, but also total elimination of Helicobacter pylori infection.[30] Patients with active duodena or gastric ulcers and those with a prior ulcer history should be tested for H. pylori.The success of H. pylori cure depends on the type and duration of therapy, patient compliance and bacterial factors such as antibiotic resistance. Patients most often fail to respond to initial H. pylori eradication therapy because of noncompliance or antibiotic resistance.As culture with antibiotic sensitivities is not routinely performed when H pylori infection is diagnosed, it is generally recommended that different antibiotics be given at higher doses for 14 days.[31]

Eradication of H pylori has proved difficult. Combination regimens that use two or three antibiotics with a proton pump inhibitor or bismuth are required to achieve adequate rates of eradication and to reduce the number of failures due to antibiotic resistance. In the United States, up to 50% of strains are resistant to metronidazole and 13% are resistant to clarithromycin. At present, experts disagree on the optimal regimen.[32]

First-Line Therapy: Triple Therapy

In areas of low clarithromycin resistance, including the United States, a 14-day course of "triple therapy, " with an oral proton pump inhibitor, clarithromycin 500 mg, and amoxicillin 1 g (or, if penicillin allergic, metronidazole 500 mg), all given twice daily for 14 days, is still recommended for first-line therapy. Unfortunately, this regimen only achieves rates of eradication >75%.[33]

Second-Line Therapy: Quadruple Therapy

With a proton pump inhibitor, bismuth, tetracycline, and metronidazole or tinidazole for 14 days is a more complicated but also more effective regimen. In a 2011 randomized, controlled trial, the per protocol eradication rates were 93% with quadruple therapy and 70% with triple therapy. Bismuth-based quadruple therapy is recommended as first line therapy for patients in areas with high clarithromycin resistance (> 20%), in patients who have previously been treated with a macrolide antibiotic, or as second-line therapy for patients whose infection persists after an initial course of triple therapy. Several studies reported eradication rates of > 90% using a 10-day sequential regimen consisting of four drugs: a proton pump inhibitor and amoxicillin for 5 days, followed by a proton pump inhibitor, clarithromycin, and tinidazole for 5 days. However, subsequent studies confirmed equivalent or superior efficacy when all four drugs were given concomitantly for 10 days (non-bismuth quadruple therapy).[34,35]

Sequential Therapy

Unfortunately, recent studies have reported lower eradication rates with sequential therapy, and a 2013 meta-analysis did not detect superiority compared with 14-day triple therapy or bismuth-based therapy, except in patients with organisms exhibiting clarithromycin resistance. Most recently, a 2013 large multicenter European controlled trial conducted in regions of high clarithromycin resistance reported 92% eradication with a 14-day quadruple therapy consisting of a proton pump inhibitor, amoxicillin, clarithromycin, and nitroimidazole.[36]

NEW TECHNIQUES

1. Non Pharmacological Treatment of Stomach Ulcers

- Spicy and fatty foods should be avoided as those generally irritate the stomach lining.
- Smoking and drink should be stopped in moderation.
- Over-the-counter pain relievers such as aspirin and NSAIDS should be avoided as those irritate the stomach lining and may also prevent a bleeding ulcer from healing.
- Excessive Iron supplements can irritate the stomach lining.
- Cabbage juice is said to increase the growth of mucin-producing cells.
- Infusion of the herb licorice is said to stimulate mucus secretion by the stomach. This should not be taken for more than a few days.
- Reducing stress and anxiety also helps reduce symptoms. Meditation, yoga, music therapy, acupuncture, massages, acupressure are all useful remedies in reducing stress
- Alsarex is a herbal ayurvedic formulation which is excellent for relieving symptoms and promoting the healing of peptic ulcers.[37]

2. Acupuncture

Acupuncture has been used traditionally for a variety of conditions related to the digestive tract, including peptic ulcers. A growing body of scientific evidence suggests that acupuncture can help reduce pain associated with endoscopy.[38]

3. Homeopathy

Although few studies have examined the effectiveness of specific homeopathic therapies, professional homeopaths may consider the following remedies for the treatment of ulcers or its symptoms, based on their knowledge and experience. Before prescribing a remedy, homeopaths take into account a person's constitutional [39]

- *Argentum nitricum* -- for abdominal bloating with belching and pain
- *Arsenicum album* -- for ulcers with intense burning pains and nausea; especially for people who cannot bear the sight or smell of food and are thirsty
- *Kali bichromicum* -- for burning or shooting abdominal pain that is worse in the hours after midnight
- *Lycopodium* -- for bloating after eating with burning that lasts for hours; especially for people who feel hungry soon after eating and wake up hungry
- *Nitric acid* -- for sharp, shooting pain that worsens at night and is accompanied by feelings of hopelessness and even fear of dying

- *Nux vomica* -- for digestive disturbances (including heartburn and indigestion) that worsen after eating; particularly for those who crave alcohol, coffee, and tobacco
- *Phosphorus* -- for burning stomach pain that worsens at night; those for whom this remedy is appropriate tend to feel very thirsty, craving cold beverages
- *Pulsatilla* -- for symptoms that vary (that is, change abruptly) and pain that gets worse from fatty foods; appropriate people are distinctly not thirsty.[38]

4. Herbs

Herbs are a way to strengthen and tone the body's systems. Work with health care provider before starting and during treatments should be done. Herbs may be used as dried extracts (capsules, powders, teas), glycerites (glycerine extracts), or tinctures (alcohol extracts). Unless otherwise indicated, make teas with 1 tsp. herb per cup of hot water.

- Cranberry *(Vacciniummacrocarpon)* 400 mg twice daily -- Some preliminary research suggests cranberry may inhibit *H. pylori* growth in the stomach. Large amounts of cranberry may be inappropriate for people who are allergic to aspirin due to the fact that cranberry contains Salicylic Acid. Cranberry extracts also can contain high levels of a chemical called oxalate, which may increase the risk of developing kidney stones.

- Mastic *(Pistacialentiscus)* standardized extract, 1,000 - 2,000 mg daily in divided dosages -- Mastic is a traditional treatment for peptic ulcers and inhibits *H. pylori* in test tubes. More studies are needed to see whether it works in humans.

- DGL-licorice (*Glycyrrhizaglabra*) standardized extract, 250 - 500 mg 3 times daily, chewed either 1 hour before or 2 hours after meals -- may help protect against stomach damage from NSAIDs. Glycyrrhizin is a chemical found in licorice that causes side effects and drug interactions. DGL is deglycyrrhizinated licorice, or licorice with the glycyrrhizin removed.[38]

5. Probiotics

Some studies have recently evaluated the role of the Saccharomyces boulardii as a coadjutant in the eradication of H. pylori and in the prevention of the secondary effects of antibiotic therapy. A meta-analysis showed that supplementation with S. boulardii significantly increased the H. pylori eradication rate and reduced the risk of overall H. pylori therapy-related adverse effects.49 In a cohort of patients in Korea who received S. boulardii for 4

weeks during and after a 1-week course of standard triple therapy, eradication rates were 10% higher than for those who did not receive the supplement.50 Other studies in which Bifidobacterium spp. and Lactobacillus acidophilus have been administered revealed no significant difference in eradication rates in patients who were infected with strains susceptible to both antibiotics and who were treated with standard triple therapy. Further studies will be necessary to clarify the exact role of the probiotics in the eradication treatment.[39]

ROLE OF SURGERY

Surgery choices

When surgery is done, it usually involves one or more of the following:

- **Truncalvagotomy or Pyloroplasty**

A vagotomy is a surgical procedure that involves removing part of or resection of the vagus nervewhich transmits messages from the person's brain to their stomach, interrupting acid secretions. [41]Pyloroplasty is surgery to widen the opening in the lower part of the stomach (pylorus) so that stomach contents can empty into the small intestine (duodenum).[40]

- **Gastrojejunostomy**

It is a surgical procedure in which an anastomosis is created between the stomach and the proximal loop of the jejunum. This is usually done either for the purpose of draining the contents of the stomach or to provide a bypass for the gastric contents.[41]

- **Billroth I and II Gastrectomy**

A Billroth I is an operation in which the pylorus is removed and the proximal stomach is anastomosed directly to the duodenum..[42]

A Billroth II is an operation in which the greater curvature of the stomach is connected to the first part of the jejunum in a side-to-side manner.[43]

- **Antrectomy**

An antrectomy removes the lower part of a person's stomach called the, 'Antrum.' The Antrum produces a hormone that stimulates the person's stomach to secrete digestive juices. The surgery enlarges the opening into the person's duodenum and small intestine, allowing contents to move more freely from their stomach.[44]

AYURVEDIC TREATMENT

Ayurveda has several effective treatment methods for ulcers. For mild symptoms of stomach or duodenal ulcers, they can be healed by just abstaining from hot/spicy foods, avoiding tobacco products, and disagreeable foods. Gastric ulcers can be controlled by SukumaraGhrita (2tsp) with warm water/milk twice a day on empty stomach. If the patient is unable to digest fats, medicine should be administered with warm water. The dosage of the medicine should also be modified depending on the digestive capacity of the patient. Hence, begin with half-a-tsp or 1 tsp and gradually increase the dosage, if the digestive power of the patient permits it. Moderate pain in cases of stomach ulcers can be controlled by ShakhaBhasma, while severe excruciating pains may require MahaShankhaVati, and the dosage should be decided by the physician. Ayucid and AvipattikarChurna is also recommended, depending on the case. Ayurvedic physicians treat cases of gastric ulcer depending on the particular dosha in a person, which varies with each individual. While medicated enema of sesame oil and asparagus oil are recommended for the Vata type, the medicated enema is done using cassia fistula and amalaki for the pita type. For individuals of kaphadosha type, vomiting is induced with sugarcane juice or salt water. Ayurvedic treatments for gastric ulcer consist of Panchakarma and Rasayana treatments, antibacterial therapies, inflammation and hyperacidity therapies, along with oral medicines and diet regulations. The doctor will decide on the treatment after careful examination and diagnosis of the patient.[45]

VACCINATION

Researchers have developed an oral vaccine against Helicobacter pylori, the bacteria responsible for peptic ulcers and some forms of gastric cancer, and have successfully tested it in mice.

Researchers from Southern Medical University in Guangdong, Guangzhou, China, have developed an oral vaccine against Helicobacter pylori, the bacteria responsible for peptic ulcers and some forms of gastric cancer, and have successfully tested it in mice. The research is published ahead of print in the journal Clinical and Vaccine Immunology.[46]

CONCLUSION

H. pylori eradication and/or antisecretory therapies are the mainstay of today's treatment strategies. In the future, it is anticipated that advances in the fields of molecular biology and genetic engineering will assist in the management of peptic ulcer disease. As the prevalence

of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, .health economics and the quality of life of patients.

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