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Research Article

H_2 ANTAGONIST AND PROTON PUMP INHIBITORS OF NEW GENERATION-PROPER CHANNELS FOR ULCER THERAPY

Devkar. Swati R*, Salunkhe.Vijay R.
Rajarambapu College of Pharmacy, Kasegaon, Tal.Walwa, Dist Sangli-415404, M.S. India.
Email: devkar.swati98@gmail.com

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Abstract

An ulcer is a localized area of erosion occurring in the stomach or duodenal lining. Ulcer is completely curable. The disease is transmitted by food, contaminated groundwater and human saliva. Due to its lethality and high prevalence it is necessary to understand the prevention, treatment and change in life style that may help its risks. Peptic ulcer disease has a major impact of health care delivery system by accounting for roughly 10% of medical costs for digestive disease.

Ulcer can promote severe unhealthy condition, cancer and death. Increasing percentage of ulcer patients attributes overall development, economic, social and clinical problems. The H2-receptor inhibitors have been used in the management of GERD, prophylaxis, and treatment of peptic and duodenal ulcer and prevention of stress-induced gastric mucosal injury. However all four H2RIs are equally effective when equipotent doses are used. PPIs are the drugs of choice for managing patients with peptic ulcers. They suppress the production of stomach acid by blocking the gastric acid pump.PPIs can be used either as part of a multidrug regimen for H. pylori, or alone for preventing and healing.

H2 antagonist and proton pump inhibitors including drugs of new generation and which are in pipeline is the perfect remedy for the ulcer treatment. Drugs of natural origin including ayurvedic, homeopathic, siddha and unani along with this medicines or an alternative to an allopathic one will be the bullet from the gun to treat this threatened disease.

Key words: Ulcer, Types, Causes, H2 Blockers**,** PPIs.

Introduction:

An ulcer is a localized area of erosion occurring in the stomach or duodenal lining. Ulcer is completely curable. Prevalence of peptic ulcers is higher in third world countries where it is estimated at about 70 percent of the population, whereas developed countries show a maximum of 40 percent ratio. The disease is transmitted by food, contaminated groundwater and human saliva. Due to its lethality and high prevalence it is necessary to understand the prevention, treatment and change in life style that may help its risks.[1] Stresses are a major risk factor as many harmful reactions apart from excess secretion of acid take place in the body owing to constant worry. [2]In United States four million individual are affected per year. The lifetime prevalence of PUD is approximately 11-14% in men and 8-11% in women. The incidence for PUD is four times more is four times more in men than women.[1] The incidence of gastrectomy in USA is 14-20% of the population with stomach cancer.[3] In India the prevalence of peptic ulcer is quite high. 4 to 10 per thousand populations suffers from peptic ulcer disease every year. Tamil Nadu, Karnataka, Andra Pradesh and Jammu & Kashmir are considered to be very high risk area.[4] In India 16% of the population undergo gastrectomy who are suffering from malignant growth of the stomach. According to a survey report on Peptic Ulcer Disease in South India the incidence of dumping syndrome accounts 10% - 20% of all the patients who has undergone gastric surgery for peptic ulcer disease.[5] Present situation efforts causes of ulcer, types of ulcer, symptoms of ulcer , types of receptors , H2 blockers and their actions ,difference between H2 antagonist and proton pump inhibitors , Proton pump inhibitors and their actions . Single drugs or fixed dose combination are more effective to treat or cure ulcer or depend on condition or as the case may be.

Ulcer and Recent Trends in Its Treatment:

An ulcer is a discontinuity or break in a bodily membrane that impedes the organ of which that membrane is a part from continuing its normal functions. The human stomach contains enumerable muscles which carry out the process of digestion and convert the different forms of food into digestive fluids. These digestive fluids are known as pepsin and hydrochloric acid. These fluids make the food digest in the stomach. The ulcer in the stomach might be the result of the disparity in the digestive fluids. The over production of pepsin or hydrochloric acid might cause ulcer. The over production of acids inside the stomach might harm the line up of the stomach and cause ulcers in the stomach. [5]

Common forms of ulcers recognized in medicine include[7:]

Ulcer (dermatology): a discontinuity of the skin or a break in the skin.

Pressure ulcers: also known as bedsores.

Genital ulcer: an ulcer located on the genital area.

Ulcerative dermatitis: a skin disorder associated with bacterial growth often initiated by self-trauma due to a possible allergic response.

Corneal ulcer: an inflammatory or infective condition of the cornea.

Mouth ulcer: an open sore inside the mouth.

Aphthous ulcer: a specific type of oral ulcer also known as a canker sore.

Peptic ulcer: - a discontinuity of the gastrointestinal mucosa (stomach ulcer).

Venous ulcer: a wound thought to occur due to improper functioning of valves in the veins.

Ulcerative sarcoidosis: a cutaneous condition affecting people with sarcoidosis.

Ulcerative lichen planus: a rare variant of lichen planus.

Ulcerative colitis: a form of inflammatory bowel disease (IBD).

Types of Ulcers [5]:

There are mainly three types of ulcer.

1. Peptic ulcer – peptic ulcer affects the lining of stomach .It happens when the ulcers are exposed to pepsin.

2. Gastric ulcer – An ulcer is called gastric when it is present in stomach.

3. Duodenal Ulcer –An ulcer is called duodenal when the ulcer is in the duodenum, it is usually found in the beginning of small intestine.

There are four types of ulcers which are found unusually. They are:

Esophageal ulcers: this type of ulcers affects the lower part of the esophagus. It might happen as a result of acid reflux.

Bleeding ulcer: a person might get bleeding ulcer if the ulcers are not treated at the right time. This causes internal bleeding which might be dangerous.

Refractory ulcer: This type of ulcer might not get healed even after three months of treatment.

Stress ulcer: Stress ulcers are found in esophagus, duodenum or stomach. This might be found in severely stressed or ill patients.

Causes[7]:

1. Genetic Factors: Helicobacter pylori - Research studies have shown that most ulcers are caused by an infection by a bacterium called Helicobacter pylori - also referred to as H. pylori. While the other factors listed below can also cause ulcers, H. pylori are now considered the cause of most ulcers. The H. pylori bacterium is found in the stomach, and along with acid secretion, can damage the tissue of the stomach and duodenum, causing inflammation and ulcers.

2. Acid: These powerful digestive fluids are believed to contribute to the formation of ulcers. In ideal situations, the stomach can protect itself from these fluids in several ways. These are: Blood circulation in the lining of the stomach, as well as cell renewal and repair, help protect the stomach.

3. Immune Abnormalities: Some experts suggest that certain individuals have abnormalities in their intestinal immune response, which allow the bacteria to injure the lining.

4. Lifestyle Factors: Life style factors like Smoking, consumption of excessive tea, excessive alcohol consumption, shift Work and Other Causes of Interrupted Sleep and Stress physical stress that can lead to ulcers are that suffered by people with injuries such as severe burns, and people undergoing major surgery.

Other Causes

NSAIDs: - NSAIDs are non-steroidal anti-inflammatory drugs. The most commonly known NSAIDs are aspirin, ibuprofen and naproxen sodium. Others are prescription NSAIDs used to treat several arthritic conditions. NSAIDs can make the stomach's defense mechanisms to fail in a couple of different ways. Peptic ulcer disease is the most common cause of UGIB in most series, accounting for over half of all cases. In the present series, 41% of patients had peptic ulcers with duodenal ulcer disease being more common than gastric ulcers.[8]

Ulcer symptoms: As the ulcer affects the stomach, it might show up several symptoms. The primary symptoms of ulcer are scorching pain in the abdomen, vomiting, blood in vomit, blood in stool, loss of appetite, nausea, fatigue, feeling weak. The symptoms of ulcer might vary from person to person. In some cases symptoms do not show up at all.

Peptic Ulcer Symptoms: Peptic ulcer shows symptoms burning pain or gnawing in stomach below the sternum, Stomach pains in the early morning hours due to hunger or between the meals, Experiencing pain while drinking coffee or orange juice and while taking aspirin, Pain after eating food or when hungry depending on the type of ulcer, Short relief from pain after taking antacid medicines, Nausea, Vomiting, Frequent burping, Chronic ulcer pain, Bloating of the stomach, Bleeding, Loss of appetite, Dizziness.

Gastric Ulcer Symptoms: A dull aching pain after eating, Increase in pain as food goes inside, No relief in the pain even after eating food. Many patients presume that the pain is caused by empty stomach and eat forcefully, Acid reflux, Heart burn, Indigestion, Nausea, Unexplained weight loss, Loss of appetite, Constant pain in the upper abdomen area below the breastbone, waking at night 3-4 hours after dinner because of dull pain, Internal bleeding seen in stool.

Duodenal Ulcer Symptoms: Heartburn, A gnawing or burning sensation in the top of stomach, inconvenience after eating, abdominal pain on taking aspirin or drinking coffee or orange juice, waking up at night due to sharp ulcer pains, vomiting, nausea, fatigue, gastrointestinal bleeding, chest pain, indigestion.

Histamine and its Receptor [9-27] Histamine occurs throughout the gastrointestinal tract, in enterochromaffin-like cells, restricted to the fundic mucosa of the stomach, mast cells and nerves. Histamine is actively produced and released in enterochromaffin-like (ECL) cells, rich in the synthesis enzyme, histidine decarboxylase (HDC), while it is mainly stored in mast cells. Histamine exerts its effects through H_1, H_2, H_3 and H_4 receptors.[7]

Histamine H_1 receptor are reported to be expressed on enterocytes, connective tissue cells, muscle layer, blood vessels, immune cells and ganglion cells of the mesenteric plexus in the human intestine. Contraction of intestinal smooth muscle is described as one of the best characterized responses mediated by H_1 receptors. Throughout the gastrointestinal tract, contractile effects are also exerted on vascular smooth muscle and on endothelial cells, this latter resulting in an increase in vascular permeability.

H_2 receptor appears to be located on parietal cells in the fluidic mucosa and they have also been found in the intestinal epithelium, immune cells and mesenteric ganglia in humans. The presence of H_3 receptor in periphery remains control H_2 receptors, located on parietal cells, are potent stimulants of gastric acid secretion. It is largely recognized that the

development of H_2-receptor antagonists revolutionized the treatment of peptic ulcer and of gastro esophageal reflux disease versial.

H_3 receptor mRNA expression is reported to be undetectable in peripheral tissues of humans and rats or alternatively to be restricted to liver and epithelia, including the mucosa of the gastrointestinal tract. Immunostaining of human intestinal tissues failed to reveal the presence of H_3 receptor. The ganglia of enteric nervous system are negative for H_3 receptor mRNA expression. The role of H_3 and H_4 receptors is less well defined. Prevention of acute gastric injury, stimulation of mucus production and increase in gastric epithelial cell proliferation in the rat appear to be regulated by H_3 receptors. The regulation of epithelial cell turnover could be of strategic importance in prevention and repair of gastric damage, suggesting a functional link between these H_3-receptor mediated effects. Proliferation is enhanced not only in the stomach but also in small intestine and colon, and the effect is selectively exerted on cells located in the proliferative compartments. H_3 receptors also regulate neurotransmission in the mesenteric plexus.

H_4 receptor mRNA appears to have a moderate to low expression in human stomach, small intestine and colon. Immunostaining revealed that enterocytes, intraepithelial neuroendocrine cells and leucocytes express the H_4 receptor in human intestinal tissue. Antagonists of H_4 receptor have been recently shown to reduce tissue damage and inflammation in a rat model of colitis, suggesting a role of the receptor in gut inflammation.

H2 Blockers[28]

H2 blockers, also called H2-receptor antagonists, are medicines that reduce the amount of acid the stomach produces by blocking one important producer of acid: histamine2. Histamine, a common chemical in the body, signals the stomach to make acid. H2 Blockers oppose histamine as action and reduce the amount of acid the stomach produces. Their four drugs that work by this mechanism in the United States are Zantac (ranitidine), Pepcid (famotidine), Tagamet (cimetidine) and Axid (nizatidine).

Different types of H2 Blockers[28]

Prescription forms: Tagamet (cimetidine), Pepcid (famotidine), Axid (nizatidine), Zantac (ranitidine).

Nonprescription (over the counter) forms: Tagamet-HB, Pepcid-AC, Axid AR, and Zantac 75.

The following is a list of H2 blockers available in both brand and generic names[29]:

Brand Name	**Generic Name**	**Rx Strength**	**OTC Name**	**OTC Strength**
Tagamet	Cimetidine	200 mg. 300 mg. 400 mg.	Tagamate HB	200 mg.
Zantac	Ranitidine	150 mg. 300 mg	Tagamet 75	75 mg.
Pepcid	Famotidine	20 mg. 40 mg.	Pepcid Ac	10 mg.
Axid	Nizatidine	150 mg. 300 mg.	Axid AR	75 mg.

Preparations:

1. Ranitidine (Zantac):- Bolus IV Dosing of Ranitidine is 50 mg IV q6-8h, Continuous IV Dosing: 6.25 mg/h IV and Oral Dosing is 150 mg PO b.i.d.
2. Cimetidine (Tagamet):- Bolus parenteral dosing: 300 mg IV or IM q6h Continuous IV Dosing: 37.5 mg/h IV and Oral Dosing: 400 mg PO b.i.d.
3. Famotidine (Pepcid):- Oral dosing: 20 to 40 mg PO b.i.d.
4. Nizatidine (Axid):-Oral dosing: 150 mg PO b.i.d.

Efficacy: a) Similar efficacy among all 4 agents. b) H2 Blockers are not as effective in Tobacco abuse Carafate and Prilosec Symptomatic relief of GERD in weeks in 70% of cases.

Adverse Effects:-Cimetidine has more drug interactions and side effects.

H2 Blockers- Different from Proton Pump Inhibitors (PPIs)[28 -33]

Both PPIs and H2 blockers suppress gastric acid secretion, but at different stages of production.. While histamine blockers block one of the first stimuli for acid production, proton pump inhibitors block the final step in the pathway of acid secretion in the stomach, resulting in greater suppression of acid. PPIs shut down the proton pumps in the stomach, H2 blockers work by blocking the histamine receptors in acid producing cells in the stomach. PPIs have a delayed onset

of action, while H2 Blockers begin working within an hour. PPIs work for a longer period of time; most up to 24 hours and the effects may last up to three days. H2 Blockers, however, usually only work up to 12 hours.

Cimetidine: A histamine congener, it competitively inhibits histamine binding to histamine H2 receptors It inhibits gastric acid secretion, as well as pepsin and gastrins output. It also blocks the activity of cytochrome P-450 .Cimetidine was the first H2 blocker introduced into clinical practice in the United States and remains a commonly used agent for treatment of duodenal and gastric ulcer and gastroesophageal reflux disease. Cimetidine was first approved for use in the United States in 1977 and is still used widely both by prescription and over-the-counter. Chemical Abstract Service number of cimetidine is 51481-61-9. Cimetidine is used for the management of acid – reflux disorders (GERD), peptic ulcer disease, heartburn, and acid indigestion. It reduces basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin. It is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastro esophageal reflux disease, and pathological hypersecretory conditions.

Ranitidine: A non-imidazole blocker of those histamine receptors that mediate gastric secretion (H2 receptors). It is used to treat gastrointestinal ulcers. Chemical Abstract Service number is 66357-35-5. It is used in the treatment of peptic ulcer disease (PUD), dyspepsia, stress ulcer prophylaxis, and gastroesophageal reflux disease. Ranitidine is a histamine H2-receptor antagonist similar to cimetidine and famotidine. These drugs are used in the treatment of dyspepsia, however their use has waned since the advent of the more effective proton pump inhibitors. Like the H1-antihistamines, the H2 antagonists are inverse agonists rather than true receptor antagonists. Oral bioavailability is approximately 50%, volume of distribution is 1.4 L/kg, 1.76 L/kg protein binding of Cimetidine is 15% it is metabolized by liver and the principal route of excretion is the urine. Half life is 2 .8-3.1hours.

Famotidine: A competitive histamine H2-receptor antagonist. Its main pharmacodynamic effect is the inhibition of gastric secretion. Chemical Abstract Service number is 76824-35-6. For the treatment of peptic ulcer disease (PUD) and gastroesophageal reflux disease (GERD). Famotidine, a competitive histamine H_2-receptor antagonist, is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. The

bioavailability of oral doses is 40-45%. Protein binding of famotidine is 15-20% it is metabolized by liver and the principal route of excretion is the urine. Half life is 2.5-3.5 hours.

Nizatidine: A histamine H2 receptor antagonist with low toxicity that inhibits gastric acid secretion. The drug is used for the treatment of duodenal ulcers. Chemical Abstract Service number is 76963-41-2 .For the treatment of acid-reflux disorders (GERD), peptic ulcer disease, active benign gastric ulcer, and active duodenal ulcer. Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H2-receptors, particularly those in the gastric parietal cells. By inhibiting the action of histamine on stomach cells, nizatidine reduces stomach acid production. Nizatidine had no demonstrable antiandrogenic action. Nizatidine competes with histamine for binding at the H_2-receptors on the gastric basolateral membrane of parietal cells. Less than 7% of an oral dose is metabolized as N2-monodes-methylnizatidine, an H2-receptor antagonist, which is the principal metabolite excreted in the urine. Other likely metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).Half life is 1-2 hours.

Roxatidine acetate: Roxatidine acetate is a specific and competitive H2 receptor antagonist. It is currently approved in South Africa under the trade name Roxit. Chemical Abstract Service No is78628-28-1For the treatment of disorders of the upper gastro-intestinal region that are due to an excess of hydrochloric acid in the gastric juice, i.e. duodenal ulcers, benign gastric ulcers. Also for prophylaxis of recurrent gastric and duodenal ulcers. Roxatidine acetate suppresses the effect of histamine on the parietal cells of the stomach (H2-receptor antagonist). This suppressive action is dose-dependent. As a result, the production and secretion, particularly of gastric acid, are reduced. Roxatidine acetate has no antiandrogenic effects and does not influence drug-metabolizing enzymes in the liver. They accomplish this by **two mechanisms**: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion have a reduced effect on parietal cells when the H2 receptors are blocked. It is well absorbed orally (80–90% bioavailability) plasma protein binding is 5-7% Roxatidine acetate is rapidly metabolized to the primary, active desacetyl metabolite. The half life is 5-6 hours.

Metiamide: Metiamide is a histamine H2-receptor antagonist developed from another H2 antagonist, burimamide. It was an intermediate compound in the development of the successful anti-ulcer drug Cimetidine. Chemical abstract

Services No is 34839-70-8 Potential in the treatment and the management of acid-reflux disorders (GERD), peptic ulcer disease, heartburn, and acid indigestion. Metiamide is a histamine H_2-receptor antagonist. It reduces basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin. Metiamide inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of Metiamide include an increase in gastric bacterial flora such as nitrate-reducing organisms. Metamide 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.

Proton Pump Inhibitors (PPIs)

Actions against ulcers - PPIs are the drugs of choice for managing patients with peptic ulcers, regardless of the cause. They suppress the production of stomach acid by blocking the gastric acid pump - the molecule in the stomach glands that is responsible for acid secretion.PPIs can be used either as part of a multidrug regimen for *H. pylori*, or alone for preventing and healing NSAID-caused ulcers. They are also useful for treating ulcers caused by Zollinger-Ellison syndrome. They are considered to be more effective than H2 blockers.

Brands approved for ulcer prevention and treatment include: Omeprazole (generic, Prilosec OTC), Esomeprazole (Nexium), Lansoprazole (Prevacid). Long-term use of PPIs may also mask the symptoms of stomach cancer and delay diagnosis.

At this time, however, there have been no reports of an increase in the incidence of stomach cancer with long-term use of these drugs. Proton pump inhibitor; binds to H+/K+-exchanging ATPase (proton pump) in gastric parietal cells resulting in blocking acid secretion.

Omeprazole: Omeprazole was first marketed in the U.S in 1989 by Astra AB, now AstraZeneca under the brand names Losec and Prilosec. An over the counter brand, Prilosec OTC, is available without prescription in the US for treatment of heartburn. The absorption of Omeprazole takes place in the small intestine and is usually completed within 3–6 hours. The systemic bioavailability of Omeprazole after repeated dose is about 60%.Omeprazole used in

treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease , laryngopharyngeal reflux (LPR) and Zollinger–Ellison syndrome.

Rabeprazole: Dose of Rabeprazole in Active Duodenal Ulcer is 20 mg PO qDay for 4 weeks .It is administration before meals swallow tablet whole, do not chew or crush.-Bioavailability of Rabeprazole is 52%and duration is about 24 hr. Half-life elimination is 1-2 hr depending on dose. Peak plasma conc. achieved within 2-5 hr. It is excreted in urine about 90% and remaining 10 % in feces. Onset of action is 2 wk (duodenal ulcer) and 4 wk (reflux esophagitis)

Esomeprazole: Dose of Esomeprazole in GERD without Erosive Esophagitis is 20 mg PO qDay for 4 weeks. It is administration before meals if patient unable to swallow capsule whole, capsule can be opened, emptied on applesauce, mixed & swallowed immediately .Bioavailability of Esomeprazole is 89-90%, food decreases AUC by 33-53%. Onset of action is 1-2 hr (gastric acid inhibition); within 4 wk (GERD). Peak Plasma conc. is achieved within 1-1.6 hr. Protein Bound is about 97% , volume of distribution is 16 L. Metabolized by liver extensively by hepatic P450 enzyme: major metabolic pathway is via CYP2C19, the rest is via CYP3A4.Metabolites: 5-hydroxyesomeprazole (inactive), esomeprazole sulfone (inactive), desmethyl- esomeprazole (activity unknown).CYP2C19 enzymes inhibited by Esomeprazole. Half-Life of Esomeprazole is 1.2-1.5 hr, total body clearance is about 9-16 L/hr and excreted urine 80% and feces 20%.

Pantoprazole: Dose of pantoprazole in Erosive Esophagitis Associated with GERD 40 mg PO day for 8-16 weeks. Bioavailability is 77%, neither food nor antacid alters bioavailability of Pantoprazole. Peak plasma conc. is achieved 2.8 hr. Protein binding is 98%, Volume of distribution is about 0.17 L/kg. Metabolized by liver extensively by hepatic P450 enzyme CYP2C19, 2nd pathway through CYP3A4. Metabolites: Desmethypantoprazole sulfate conjugate (activity unknown).Half life of pantoprazole is 1 hr. Total body clearance is about 7.6-14 L/hr and renal clearance is about 0.1 L/hr/kg. It is excreted in 71-82% urine; 18-20% feces.

Proton pump inhibitors are widely used in patients with non-variceal UGIB, and in this study, 91% of patients received PPI therapy. In a recent study, PPI was given in 57.5% and combined with histamine -2 receptor antagonists in another 10%.

Conclusion

Majority of peoples in India and other developing countries are affected by ulcer which has impact on overall health. Although there are remedies to solve such a problems, if not cured, prevented or treated properly, may create unhealthy condition, cancer or death. severity of ulcer and increasing number of ulcer patients have economic , social and clinical burden on family as well as overall development of country . Drugs of new generation including H2 antagonist and proton pump inhibitors highlight the importance of curative and preventive measurement of ulcer. Mostly H2 antagonist and proton pump inhibitors in pipeline will be missile against the same.

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Corresponding Author:

Devkar. Swati R*,

Email: *devkar.swati98@gmail.com*