PRESCRIPTION PATTERN OF ACID SUPPRESSIVE MEDICATIONS IN BANGLADESH

A THESIS PAPER SUBMITTED TO THE DEPARTMENT OF PHARMACY, EAST WEST UNIVERSITY BANGLADESH IN PARTIAL FULLFILLMENT OF THE REQUIRMENTS FOR THE DEGREE OF MASTER OF PHARMACY (M.PHARM)

Submitted By

Tourat Hossain

ID: 2011-1-79-006

Submission Date: JULY, 2012

Department of Pharmacy

East West University

CERTIFICATE

This is to certify that, the thesis, entitled "**Prescription Pattern of Acid Suppressive Medications in Bangladesh"**, Submitted by Tourat Hossain, ID No.2011-1-79-006, Department of Pharmacy, East West University Bangladesh, has been accepted as satisfactory for partial fulfillment of the requirements for the Degree of Master of Pharmacy (M.Pharm) and approved as its style and content.

Sufia Islam Ph.D
Associate Professor
Chairperson
Department of Pharmacy
East West University
Aftabnagar, Dhaka

CERTIFICATE

This is to certify that the thesis, entitled "**Prescription Pattern of Acid Suppressive Medications in Bangladesh"** submitted to the Department of Pharmacy, East West University Bangladesh for the partial fulfill of the requirements for the degree of master of pharmacy (M.Pharm) was carried out by Md. Tourat Hossain (ID: 2011-1-79-006) under my guidance and supervision and that no part of the thesis has been submitted for any other degree. I further certify that all the sources of information and other facilities available of this connection are duly acknowledgement.

Mrs. Farhana Rezwan
Senior Lecturer
Department of Pharmacy
East West University, Bangladesh.
Supervisor

ACKNOWLEDGEMENT

I would like to express my gratitude to all those who gave me the possibility to complete this project. I would like to express my sincere thanks to my supervisor and respected madam **Mrs. Farhana Rezwan**, Senior Lecturer, Department of Pharmacy, East West University Bangladesh for giving me permission to commence this thesis related to my job/portfolio and encouraged me to go ahead with my thesis work. I am also deeply indebted to her, whose help, stimulating suggestions and encouragement helped me in all the time of research and writing of this paper.

I also wish to thank my colleagues and the office staffs and all of my friends for their great support and inspiration during my project work.

Finally, I am profoundly indebted to the Almighty for providing me the strength and perseverance to carry out the whole work in time.

Dedicated to My Beloved Parents

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List of Abbreviation

AIDS	Acquired Immunodeficiency Syndrome
Bd	Twice Daily *(bis diem)*
BP	Blood Pressure
GERD	Gastroesophageal Reflux Disease;
GIT	Gastrointestinal Tract
GORD	Gastro-Oesophageal Reflux Disease
H2RAs	H2 receptor antagonists
NDTI	National Disease and Therapeutic Index
NERD	Non-Erosive Reflux Disease
NR	Not Reported
NS	Not Significant
NSAID	Nonsteroidal Anti-Inflammatory Drug
NUD	Non-Ulcer Dyspepsia
OTC	Over the Counter
PPI	Proton Pump Inhibitor

ABSTRACT

Gastrointestinal disorders, specifically acid-related disorders including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and dyspepsia are very common in Bangladesh. About 16% of patients are suffering from gastrointestinal acid related disorders .According to 4P data (Product, Place, price & Promotion) from 4P Marketing Consultancy, Bangladesh, June, 2012 it is reported that 16.71% of patients are suffering from gastrointestinal acid related disorders. Their findings come from prescription-based study (7 lac prescriptions) .This data may focus on the prevalence of acid-related disorders in Bangladesh like Peptic ulcer diseases, Dyspepsia, etc. The results demonstrated 16.71% of this patient population had acid-related disorders, where male patients is 15.42%, Female patients is 17.73% and different aged group patients is in different percentages. Current treatment guidelines for acid-related diseases (ARDs) recommend first-line treatment with a proton pump inhibitor (PPI) to reduce gastric acid production. PPIs are indicated in the management of gastroesophageal reflux disease (reflux esophagitis, nonerosive reflux disease), peptic ulcer (gastric and duodenal ulcer, non-steroidal anti-inflammatory drug (NSAID)-associated ulcer, bleeding ulcer), functional dyspepsia, and in association with Helicobacter pylori eradication therapy when needed. Currently, PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are widely used for the treatment of ARDs. All 5 PPIs are effective. However, there are differences in PPI pharmacokinetic and pharmacodynamic profiles that might influence their clinical utility. In Bangladesh total anti ulcerants market value is very large with high growth. According to IMS data, 4Q 2011, Total antiulcerant market is about 12090 million Tk with 31.64 % growth. Antiulcerant market share is 14%. Absolutely this share is very high. Whereas only Proton Pump inhibitors' market is 9500 million taka with 37.71 % growth.

Chapter One:

INTRODUCTION

REVIEW

Gastrointestinal acid-related diseases (ARDs) are very common problem in Bangladesh as well as in the World. Acid-related diseases caused by imbalance of the cells of the gastric gland and their secretions. Most common is hyperacidity. Clients report symptoms of overproduction of HCl by the parietal cells are as indigestion, sour stomach, heartburn, acid stomach. Gastrointestinal disorders, specifically acid-related disorders includes- Peptic ulcer disease (PUD), Gastroesophageal reflux disease (GERD), Dyspepsia.

About 16% of patients are suffering from gastrointestinal acid related disorders.(According to 4P Marketing Consultancy data)

At past Antacids and H_2-blockers were used in treating those diseases. Now-a-days proton pump inhibitors are very popular and widely prescribed for their better efficacy and safety profiles. Different types of PPIs are now positioned in different type and group of patients.

The objective of this study is to gain a better understanding of prescription pattern of Anti-ulcerants and the usage of these agents in different types of patients with different types of gastrointestinal acid related disorders.

A comparison of Esomeprazole Lansoprazole, Omeprazole, Pantoprazole, and Rabeprazole:

Five proton pump inhibitors (PPIs) are currently marketed in various parts of the world, and all of these (Esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) are available for prescription use in the United States. As a therapeutic group, the PPIs are highly useful for the relief of symptoms and healing of gastroesophageal reflux disease, gastric and duodenal ulcer disease, eradication of Helicobacter pylori infection, prevention and treatment of nonsteroidal antiinflammatory drug (NSAID)-associated damage, management of hypersecretory states such as Zollinger-Ellison syndrome, and care of patients with non-variceal upper gastrointestinal bleeding, or non-ulcer dyspepsia. The pathophysiologic basis of these management benefits lies in the potent gastric acid inhibitory effects of the PPIs. There are differences between the PPIs in their pharmacokinetics, pharmacodynamics, influence by food and antacids, clinical efficacy, and potential for drug interactions. It is not always clear whether these often subtle variations are necessarily of clinical importance. The physician's choice of one PPI over another must rest with her/his interpretation of the clinical importance of the generally small differences between PPIs, their approval for treatment of

specific clinical indications within the physician's practice jurisdiction, and the strength of the evidence based on the quantity and quality of the supporting clinical trials.

Comparative studies among PPIs

Table 1.1: Comparative studies among PPIs

Groups	Indications	Side efffects
Esomeprazole-is a PPI that suppresses gastric acid secretion by specific inhibition of the H+ /K+ ATPase in the gastric parietal cell.	Treatment of Gastroesophageal Reflux Disease with or withowt Oesophagitis Including Erosions and Ulcerations, Peptic Ulcer.	Headache, diarrhea, nausea, gas, decreased appetite, constipation, dry mouth, and abdominal pain.
Lansoprazole- inhibits gastric acid secretion by inhibiting the H+/K+ ATPase, which is also known as proton pump. Both basal and stimulated acid are inhibited.	Treatment of Pathological Hypersecretory Conditions eg. Zollinger-Ellision Syndrome. Acid Related Dyspepsia.peptic ulcer, Treatment of GERD, Treatment of NSAID Associated Ulceration.	dry mouth, insomnia, drowsiness, blurred vision, rash, pruritus
Omeprazole- Suppresses gastric acid secretion by specific inhibition of the enzyme system H+/K+ ATPase present on the secretory surface of the gastric parietal cell.	NSAID associated Duodenal ore Gastric Ulcer and Gastroduodenal Erosions, Prophylaxis of acid of acid aspiration during anaesthesia,Acid related dyspepsia, peptic ulcer,Eradication of *H.pylori* infection, Zollinger-Ellision Syndrome etc	Headache, diarrhea, nausea, constipation, flatulence, abdominal colic, paraesthesia, dizziness.
Pantoprazole-inhibits H+/K+ ATPase pump function thereby reducing gastric acid secretion. It also has a role in the eradication of *H.pylori*.	Treatment of Gastroesophageal Reflux Disease with or without Oesophagitis Including Erosions and Ulcerations, Peptic Ulcer. Eradication of *H.pylori.*	Diarrhea, dizziness, pruritis, skin rashes,GIT infections, chest pain, headache, , nausea, anxiety, insomnia oedema etc.

Rabeprazole- is a PPI that suppresses gastric acid secretion by specific inhibition of the H+ /K+ ATPase in the gastric parietal cell.	Treatment of GERD, Treatment of Pathological Hypersecretory Conditions eg. Zollinger-Ellision Syndrome, Eradication of *H.pylori*, Treatment of Active peptic Ulcer disease.	Headache, diarrhea,rash, infection and flu-like syndrome, dizziness,fatigue, constipation, nausea and vomiting.

So, clarify the above data it is clear that the indication of PPIs are almost same among them, but they are slightly different on the basis of their dosage and acceptable for their relative less side effects.[1]

Future Research and New Generations of PPIs

Tenatoprazole (TU-199), an imidazopyridine proton pump inhibitor, is a novel compound that has been designed as a new chemical entity with a substantially prolonged plasma half-life (7h), but otherwise has similar activity as other PPIs. The difference in the structural backbone of tenatoprazole compared to bensimidazole PPIs, is its imidazopyridine moiety, which reduces the rate of metabolism, allowing a longer plasma residence time but also decreases the pKa of the fused imidazole N as compared to the current PPIs. Tenatoprazole has the same substituents as omeprazole, the methoxy groups at position 6 on the imidazopyridine and at position 4 on the pyridine part as well as two methyl groups at position 3 and 5 on the pyridine. The bioavailability of tenatoprazole is double for the S-tenatoprazole sodium salt hydrate form when compared to the free form in dogs. This increased bioavailability is due to differences in the crystal structure and hydrophobic nature of the two forms, and therefore its more likely to be marketed as the pure S-enantiomer.[2]

1.1 INTRODUCTION:

Gastrointestinal disorders, specifically acid-related disorders including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and dyspepsia are very common in Bangladesh. About 16% of patients are suffering from gastrointestinal acid related disorders .According to 4P data (Product, Place, price & Promotion) from 4P Marketing Consultancy, Bangladesh, June, 2012 it is reported that 16.71% of patients are suffering from gastrointestinal acid related disorders. Their findings come from prescription-based study (7 lac prescriptions) .This data may focus on the prevalence of acid-related disorders in Bangladesh like Peptic ulcer diseases, Dyspepsia, etc. The results demonstrated 16.71% of this patient population had acid-related disorders, where male patients is 15.42%, Female patients is 17.73% and different aged group patients is in different percentages. All are given in Table-1.

Current treatment guidelines for acid-related diseases (ARDs) recommend first-line treatment with a proton pump inhibitor (PPI) to reduce gastric acid production. PPIs are indicated in the management of gastroesophageal reflux disease (reflux esophagitis, nonerosive reflux disease), peptic ulcer (gastric and duodenal ulcer, non-steroidal anti-inflammatory drug (NSAID)-associated ulcer, bleeding ulcer), functional dyspepsia, and in association with Helicobacter pylori eradication therapy when needed. Currently, PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole) are widely used for the treatment of ARDs. All 5 PPIs are effective. However, there are differences in PPI pharmacokinetic and pharmacodynamic profiles that might influence their clinical utility. Rabeprazole is a useful option for the treatment of acid-related diseases due to its rapid onset of acid inhibition and few drug interactions. The use of PPI monotherapy was highest among patients with peptic ulcer diseases. Prescription share of some acid suppressing medication in PUD is given in Table-02.

In Bangladesh total anti ulcerants market value is very large with high growth. According to IMS data, 4Q 2011, Total antiulcerant market is about 12090 million Tk with 31.64 % growth. Antiulcerant market share is 14%. Absolutely this share is very high. Whereas only Proton Pump inhibitors' market is 9500 million taka with 37.71 % growth. Total market scenario of antiulcerant is given in Table-03

Table-1.2: prevalence of acid-related disorders in Bangladesh

Name	Nat	Male	Female	0-5 years	6-10 years	11-30 years	31-50 years	51 years+
Gastrointestinal gas	0.29	0.38	0.22	1.19	0.11	0.14	0.19	0.17
Peptic ulcer diseases (PUD)	1.35	1.18	1.48	0.09	0.34	1.37	1.79	1.76
Peptic ulcer diseases (PUD)-moderate	0.61	0.55	0.66	0.13	0.14	0.68	0.81	0.66
Peptic ulcer diseases (PUD)-severe	0.14	0.15	0.13	0.04	0.10	0.13	0.18	0.17
Peptic ulcer diseases (PUD)-prophylaxis for drug induced	5.37	5.30	5.43	0.38	2.63	5.51	7.25	6.26
Peptic ulcer diseases (PUD)-not mentioned	5.11	4.69	5.44	0.48	1.93	5.95	5.77	6.11
Symptoms-abdominal pain	3.53	2.91	4.02	0.98	4.15	4.79	3.91	2.95
Symptoms-GI bleeding	0.01	0.02	0.01	0.02	0.00	0.02	0.01	0.01
Dyspepsia	0.29	0.25	0.33	0.07	0.10	0.38	0.36	0.26
Total	16.71	15.42	17.73	3.37	9.50	18.97	20.26	18.34

Table-1.3: Prescription share of some acid suppressing medication in PUD

DISEASES	National Rx Share (%)	No. of Rx
Peptic ulcer diseases (mild)		
Domperidone-oral solid	45.63	8949 Rx
Omeprazole-oral solid	13.03	
Esomeprazole-oral solid	12.66	
Pantoprazole-oral solid	4.98	
Rabeprazole-oral solid	3.96	
Peptic ulcer diseases (pud)-moderate		
Esomeprazole-oral solid	22.89	4050 Rx
Omeprazole-oral solid	18.89	
Domperidone-oral solid	14.30	
Pantoprazole-oral solid	7.46	
Rabeprazole-oral solid	6.32	
Peptic ulcer diseases (pud)-severe		
Omeprazole-oral solid	17.99	906 Rx
Esomeprazole-oral solid	16.00	
Domperidone-oral solid	12.80	
Magaldrate+simethicone-oral liquid	6.62	
Pantoprazole-oral solid	5.08	
Peptic ulcer diseases (pud)-prophylaxis for drug induced		
Omeprazole-oral solid	47.70	35641 Rx
Esomeprazole-oral solid	23.92	
Pantoprazole-oral solid	11.69	
Rabeprazole-oral solid	6.18	
Ranitidine-oral solid	5.03	

Table-1.4: Total Market Scenario of Anti-ulcerants in Bangladesh

Source: IMS 4Q 2011

Name	Value (In BDT)	Share (%)	Growth (%)
ANTIULCERANTS	12,094,984,403	100.00	31.64
ACID PUMP INHIBITORS	9,502,102,463	78.56	37.71
OMEPRAZOLE	5,089,228,932	53.56	27.12
ESOMEPRAZOLE	2,260,894,212	23.79	57.49
PANTOPRAZOLE	1,412,973,928	14.87	39.82
RABEPRAZOLE	568,386,055	5.98	93.46
LANSOPRAZOLE	170,619,336	1.80	8.93
H2 ANTAGONISTS	2,517,740,154	20.82	12.38
RANITIDINE	2,450,049,037	97.31	12.78
FAMOTIDINE	67,374,749	2.68	1.73
SUCRALFATE	27,210,183	0.22	59.13
ANTACIDS ANTIFLATULENTS	830,477,386	6.87	23.74
ANTACIDS + ANTIFLATULENTS	591,084,462	71.17	33.76
PLAIN ANTACIDS	187,699,185	22.60	0.61
PLAIN ANTIFLATULENTS	51,693,740	6.22	21.07
SIMETICONE	48,492,334	0.40	29.50

1.2 GASTROINTESTINAL DISORDER:

Acid-Related Diseases:

Caused by imbalance of the cells of the gastric gland and their secretions. Most common is hyperacidity. Clients report symptoms of overproduction of HCl by the parietal cells as indigestion, sour stomach, heartburn, acid stomach.[3, 4]

1.2.1 PUD OR PEPTIC ULCER DISEASE

A peptic ulcer, also known as PUD or peptic ulcer disease, is the most common ulcer of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. It is defined as mucosal erosions equal to or greater than 0.5 cm. As many as 70–90% of such ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach; however, only 40% of those cases go to a doctor. Ulcers can also be caused or worsened by drugs such as aspirin, ibuprofen, and other NSAIDs.

Four times as many peptic ulcers arise in the duodenum—the first part of the small intestine, just after the stomach—as in the stomach itself. About 4% of gastric ulcers are caused by a malignant tumor, so multiple biopsies are needed to exclude cancer. Duodenal ulcers are generally benign.[5]

Classification (By Region/Location)

- Duodenum (called duodenal ulcer)
- Oesophagus (called esophageal ulcer)
- Stomach (called gastric ulcer)
- Meckel's diverticulum (called Meckel's diverticulum ulcer; is very tender with palpation)[6]

1.2.1a Signs and symptoms:

Symptoms of a peptic ulcer can be abdominal pain, classically epigastric with severity relating to mealtimes, after around three hours of taking a meal (duodenal ulcers are classically relieved by food, while gastric ulcers are exacerbated by it); bloating and abdominal fullness; waterbrash (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 oxidized iron from hemoglobin); rarely, an ulcer can lead to a gastric or duodenal perforation, which leads to acute peritonitis. This is extremely painful and requires immediate surgery.[7]

1.2.1b Complications

- Gastrointestinal bleeding is the most common complication. Sudden large bleeding can be life-threatening. It occurs when the ulcer erodes one of the blood vessels, such as the gastroduodenal artery.
- Perforation (a hole in the wall) often leads to catastrophic consequences. Erosion of the gastro-intestinal wall by the ulcer leads to spillage of stomach or intestinal content into the abdominal cavity. Perforation at the anterior surface of the stomach leads to acute peritonitis, initially chemical and later bacterial peritonitis. The first sign is often sudden intense abdominal pain. Posterior wall perforation leads to bleeding due to involvement of gastroduodenal artery that lies posterior to the 1st part of duodenum.
- Penetration is when the ulcer continues into adjacent organs such as the liver and pancreas.
- Scarring and swelling due to ulcers causes narrowing in the duodenum and gastric outlet obstruction. Patient often presents with severe vomiting.
- Cancer is included in the differential diagnosis (elucidated by biopsy), Helicobacter pylori as the etiological factor making it 3 to 6 times more likely to develop stomach cancer from the ulcer.[8]

1.2.2 GERD OR GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD), gastro-oesophageal reflux disease (GORD), gastric reflux disease, or acid reflux disease is a chronic symptom of mucosal damage caused by stomach acid coming up from the stomach into the esophagus.

GERD is usually caused by changes in the barrier between the stomach and the esophagus, including abnormal relaxation of the lower esophageal sphincter, which normally holds the top of the stomach closed; impaired expulsion of gastric reflux from the esophagus, or a hiatal hernia. These changes may be permanent or temporary. GERD is a chronic condition.

Once it begins, it usually is life-long. If there is injury to the lining of the esophagus (esophagitis), this also is a chronic condition. Moreover, after the esophagus has healed with treatment and treatment is stopped, the injury will return in most patients within a few months. Once treatment for GERD is begun, therefore, it usually will need to be continued indefinitely although it is argued that in some patients with intermittent symptoms and no esophagitis, treatment can be intermittent and done only during symptomatic periods.[9]

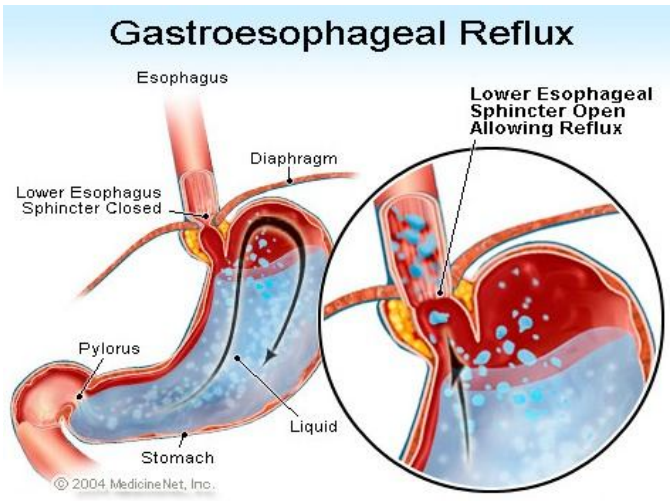


Fig. 1.1: GERD

1.2.2a Causes of Acid Reflux (GERD)

No one knows the exact cause of gastroesophageal reflux. The following are contributing factors that weaken or relax the lower esophageal sphincter, making reflux worse:

Lifestyle: Use of alcohol or cigarettes, obesity, poor posture (slouching)

Medications: Calcium channel blockers, theophylline (Tedral, Hydrophed, Marax, Bronchial, Quibron), nitrates, antihistamines

Diet: Fatty and fried foods, chocolate, garlic and onions, drinks with caffeine, acid foods such as citrus fruits and tomatoes, spicy foods, mint flavorings

Eating habits: - Eating large meals, eating soon before bedtime

Other medical conditions: Hiatal hernia, pregnancy, diabetes, rapid weight gain

1.2.2b Acid Reflux (GERD) Symptoms

Persistent *HEARTBURN* is the most common symptom of GERD. Heartburn is a burning pain in the center of the chest, behind the breastbone. It often starts in the upper abdomen and spreads up into the neck. The pain can last as long as 2 hours. Heartburn is usually worse after eating. Lying down or bending over can bring on heartburn or make it worse. The pain usually does not start or get worse with physical activity.Heartburn is sometimes referred to as acid indigestion. Not everyone with GERD has heartburn.

Other symptoms of GERD include the following:

- Regurgitation of bitter acid up into the throat while sleeping or bending over
- Bitter taste in the mouth
- Persistent dry cough
- Hoarseness (especially in the morning)
- Feeling of tightness in the throat, as if a piece of food is stuck there
- Wheezing

The most common symptoms in children and infants are repeated vomiting, coughing, and other respiratory problems.[10]

1.2.3 DYSPEPSIA

Dyspepsia, also known as upset stomach or indigestion, refers to a condition of impaired digestion. It is a medical condition characterized by chronic or recurrent pain in the upper abdomen, upper abdominal fullness and feeling full earlier than expected when eating. It can be accompanied by bloating, belching, nausea, or heartburn. Dyspepsia is a common problem, and is frequently associated with, gastroesophageal reflux disease (GERD) or gastritis. In a small minority it may be the first symptom of peptic ulcer disease (an ulcer of the stomach or duodenum) and occasionally cancer. Hence, unexplained newly onset dyspepsia in people over 55 or the presence of other alarming symptoms may require further investigations.

1.2.3a Signs and symptoms

The characteristic symptoms of dyspepsia are upper abdominal pain, bloating, fullness and tenderness on palpation. Pain worsened by exertion and associated with nausea and perspiration may also indicate angina.

Occasionally dyspeptic symptoms are caused by medication, such as calcium antagonists (used for angina or high blood pressure), nitrates (used for angina), theophylline (used for chronic lung disease), bisphosphonates, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs, used as painkillers).

The presence of gastrointestinal bleeding (vomit containing blood), difficulty swallowing, loss of appetite, unintentional weight loss, abdominal swelling and persistent vomiting are suggestive of peptic ulcer disease or malignancy, and would necessitate urgent investigations.

Functional dyspepsia (previously called nonulcer dyspepsia) is dyspepsia "without evidence of an organic disease that is likely to explain the symptoms". Functional dyspepsia is estimated to affect about 15% of the general population in western countries.[11]

1.2.4 *Helicobacter pylori (H. pylori)*

Helicobacter pylori (H. pylori) is a bacterium that causes chronic inflammation of the inner lining of the stomach (gastritis) in humans. This bacterium also is considered as a common cause of ulcers worldwide; as many as 90% of people with ulcers have detectable organisms.

H. pylori infection is most likely acquired by ingesting contaminated food and water, and through person to person contact. In the United States, about 30% of the adult population is infected (50% of infected persons are infected by the age of 60), but the prevalence of infection is decreasing because there is increasing awareness about the infection, and treatment is common. About 50% of the world population is estimated to have detectable *H. pylori* in their gastrointestinal tract (GI tract, but stomach, mainly).

1.2.4a The symptoms of *H. pylori* infections

Most individuals infected with H. pylori have few or no symptoms. They may experience a few episodes of gastritis (minor belching, bloating, nausea, vomiting, abdominal discomfort), but little or nothing else. Often, these symptoms simply cease. However, those individuals

who have a more serious infection exhibit symptoms of stomach and duodenal ulcers or gastritis which include the following:

- ✓ Abdominal pain and/or discomfort that usually does not wax and wane
- ✓ Nausea and vomiting sometimes with blood or coffee-ground like vomitus
- ✓ Dark or tar-like stools (black color of feces due to bleeding ulcers)
- ✓ Fatigue
- ✓ Low red blood cell count due to bleeding
- ✓ Full feeling after a small amount of food; decreased appetite that is more constant
- ✓ Symptoms of black, tarry stools and fatigue should cause a person to seek medical help or go to an emergency department to be evaluated for intestinal bleeding.[12]

1.2.5 Zollinger–Ellison syndrome

Zollinger–Ellison syndrome is a triad of gastric acid hypersecretion, severe peptic ulceration, and non-beta cell islet tumor of pancreas (gastrinoma). In this syndrome increased levels of the hormone gastrin are produced, causing the stomach to produce excess hydrochloric acid. Often the cause is a tumor (gastrinoma) of the duodenum or pancreas producing the hormone gastrin. Gastrin then causes an excessive production of acid which can lead to peptic ulcers in almost 95% of patients.

1.2.5a Pathophysiology

Gastrin works on stomach parietal cells causing them to secrete more hydrogen ions into the stomach lumen. In addition, gastrin acts as a trophic factor for parietal cells, causing parietal cell hyperplasia. Thus there is an increase in the number of acid-secreting cells, and each of these cells produces acid at a higher rate. The increase in acidity contributes to the development of multiple peptic ulcers in the stomach and duodenum (small bowel).

1.2.5b Symptoms

Chronic Diarrhea, Pain in the Esophagus, especially between and after meals at night, Nausea, Wheezing, Vomiting Blood (digested Blood), Malnourishment, Loss of weight due to loss of appetite.[13]

1.3 AVAILABLE ACID-CONTROLLING AGENTS IN BANGLADESH

- *Antacids*
- *H_2 antagonists*
- *Proton pump inhibitors*

1.3.1 ANTACIDS:

An antacid is a substance which neutralizes stomach acidity.

1.3.1a Mechanism of Action:

Antacids either directly neutralize acidity, increasing the pH, or reversibly reduce or block the secretion of acid by gastric cells to reduce acidity in the stomach. When gastric hydrochloric acid reaches the nerves in the gastrointestinal mucosa, they signal pain to the central nervous system. This happens when these nerves are exposed.

- Antacids promote gastric mucosal defense mechanisms.
- By secretion of:
    - *Mucus*: protective barrier against HCl
    - *Bicarbonate*: helps buffer acidic properties of HCl
    - *Prostaglandins*: prevent activation of proton pump which results in ⇓ HCl production
- Antacids DO NOT prevent the over-production of acid
- Antacids DO neutralize the acid once it's in the stomach

1.3.1b Antacids: Drug Effects:

Reduction of pain associated with acid-related disorders

- Raising gastric pH from 1.3 to 1.6 neutralizes 50% of the gastric acid
- Raising gastric pH 1 point (1.3 to 2.3) neutralizes 90% of the gastric acid
- Reducing acidity reduces pain

1.3.1c Antacids: Aluminum Salts:

Forms: carbonate, hydroxide

- Have constipating effects
- Often used with magnesium to counteract constipation

1.3.1d Antacids: Magnesium Salts

Forms: carbonate, hydroxide, oxide, trisilicate

- Commonly cause diarrhea; usually used with other agents to counteract this effect
- Dangerous when used with renal failure —the failing kidney cannot excrete extra magnesium, resulting in hypermagnesemia

1.3.1e Antacids: Calcium Salts

Forms: many, but carbonate is most common

- May cause constipation
- Their use may result in kidney stones
- Long duration of acid action may cause increased gastric acid secretion (hyperacidity rebound)
- Often advertised as an extra source of dietary calcium

1.3.1f Antacids: Sodium Bicarbonate

- Highly soluble
- Buffers the acidic properties of HCl
- Quick onset, but short duration
- May cause metabolic alkalosis
- Sodium content may cause problems in patients with HF, hypertension, or renal insufficiency (fluid retention)

1.3.1g Antacids and Antiflatulents

Antiflatulents: used to relieve the painful symptoms associated with gas

Several agents are used to bind or alter intestinal gas and are often added to antacid combination products

1.3.1h Simethicone

- Alters elasticity of mucus-coated bubbles, causing them to break
- Used often, but there are limited data to support effectiveness[14]

Table-1.5: Available Antacids top brands in Bangladesh

BRAND NAME	COMPANY	AVAILABLE DOSAGE FORM	VALUE	SHARE (%)	GROWTH (%)
ANTACIDS ANTIFLATULENTS			830,477,386	6.43	23.74
ANTACIDS + ANTIFLATULENTS			591,084,462	71.17	33.76
Entacyd plus	Square	Suspension and Tablet	305,592,282	51.70	18.94
Novelta	Orion pharma		84,076,899	14.22	46.19
Marlox plus	Incepta		82,873,527	14.02	176.39
Flatameal	Beximco		40,260,832	6.81	-0.33
Antanil-plus	Ibn sina		19,743,933	3.34	16.06
PLAIN ANTACIDS			187,699,185	22.60	0.61
Entacyd	Square	Suspension and tablet	72,007,393	58.00	-4.70
Lactameal	Beximco		14,863,513	11.97	33.51
Oxecone	Acme		13,433,705	10.82	13.96
Antanil	Ibn sina		12,230,878	9.85	17.17
Jpdrox	Jayson		979,610	0.79	-61.00
Marlox	Incepta		4,290,740	32.15	77.92
Acidrox-m	syntho labs		995,361	7.46	-36.51
Magacil	Opsonin		339,889	2.55	999.00

PLAIN ANTIFLATULANT			51,693,740	6.22	21.07
Simeticone	Sonear	Drops paed.	48,492,334	93.81	29.50
Flacol	Square		29,710,345	61.27	22.54
Gasnil	Eskaef		2,905,789	5.99	11.06
Semecon	Drug- International		2,738,197	5.65	31.07
Flatulex	Opsonin		2,377,532	4.90	102.59
Lefoam	Incepta		2,020,983	4.17	21.11

1.3.2 H_2 ANTAGONISTS

The H_2 receptor antagonists are a class of drugs used to block the action of histamine on parietal cells in the stomach, decreasing the production of acid by these cells. H_2 antagonists are used in the treatment of dyspepsia, although they have been surpassed in popularity by the more effective proton pump inhibitors. In the United States, all four FDA-approved members of the group—cimetidine, ranitidine, famotidine, and nizatidine—are available over the counter in relatively low doses.[15]

Table-1.6: Available H_2 antagonists (top brands) in Bangladesh

BRAND	COMPANY	AVAILABLE DOSAGE FORM	VALUE	SHARE	GROWTH
H2 ANTAGONISTS			2,517,740,154	20.82	12.38
RANITIDINE			2,450,049,037	97.31	12.78
NEOTACK	Square	150 mg Tablet, 75 mg/5 ml syrup, 50 mg Inj.	679,099,068	27.72	17.59
NEOCEPTINR	Beximco		629,038,225	25.67	4.51
RANITID	Opsonin		300,428,672	12.26	13.41
RANIDIN	ACME		160,177,282	6.54	11.16
PEPTIL-H	Eskayef		137,966,006	5.63	47.86

FAMOTIDINE			67,374,749	2.68	1.73
SERVIPEP	SANDOZ	20 mg & 40 mg Tablet	38,026,948	56.44	1.56
FAMOTACK	Square		9,783,075	14.52	2.02
YAMADIN	Beximco		8,340,581	12.38	8.15
FAMOTID	Drug- Int.		4,734,058	7.03	10.00
AMODIN	ACME		3,298,960	4.90	-22.54

1.3.2.1 RANITIDINE:

Ranitidine is in a group of drugs called histamine-2 blockers. Ranitidine works by reducing the amount of acid your stomach produces.

Ranitidine is used to treat and prevent ulcers in the stomach and intestines. It also treats conditions in which the stomach produces too much acid, such as Zollinger-Ellison syndrome. Ranitidine also treats gastroesophageal reflux disease (GERD) and other conditions in which acid backs up from the stomach into the esophagus, causing heartburn.

1.3.2.1a Indication of Ranitidine:

- Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
- Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
- The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
- Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
- Maintenance therapy for gastric ulcer patients at reduced dosage after healing of acute ulcers. Placebo-controlled studies have been carried out for 1 year.

- Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ranitidine 150 mg twice daily.
- Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with Ranitidine 150 mg 4 times daily.
- Maintenance of healing of erosive esophagitis. Placebo-controlled trials have been carried out for 48 weeks.

1.3.2.1b Dosage & Administration:

Active Duodenal Ulcer:

The current recommended adult oral dosage of Ranitidine for duodenal ulcer is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL of syrup (4 teaspoonfuls of syrup equivalent to 300 mg of ranitidine) once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see Clinical Trials: Active Duodenal Ulcer). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg twice daily is as effective as the 150-mg dose.

Maintenance of Healing of Duodenal Ulcers

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily. In some patients it may be necessary to administer Ranitidine 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer:

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily.

Maintenance of Healing of Gastric Ulcers:

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at bedtime.

GERD:

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily.

Erosive Esophagitis:

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) 4 times daily.

Maintenance of Healing of Erosive Esophagitis:

The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily.

Pediatric Use:

The safety and effectiveness of Ranitidine have been established in the age-group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of Ranitidine in neonatal patients (less than 1 month of age) to make dosing recommendations.

Treatment of Duodenal and Gastric Ulcers:

The recommended oral dose for the treatment of active duodenal and gastric ulcers is 2 to 4 mg/kg twice daily to a maximum of 300 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

Maintenance of Healing of Duodenal and Gastric Ulcers:

The recommended oral dose for the maintenance of healing of duodenal and gastric ulcers is 2 to 4 mg/kg once daily to a maximum of 150 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

Treatment of GERD and Erosive Esophagitis:
Although limited data exist for these conditions in pediatric patients, published literature supports a dosage of 5 to 10 mg/kg/day, usually given as 2 divided doses.

Dosage Adjustment for Patients with Impaired Renal Function:
On the basis of experience with a group of subjects with severely impaired renal function treated with Ranitidine, the recommended dosage in patients with a creatinine clearance < 50 mL/min is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Elderly patients are more likely to have decreased renal function, therefore caution should be exercised in dose selection, and it may be useful to monitor renal function

1.3.2.1c Precautions

General:
Symptomatic response to therapy with ZANTAC (ranitidine HCl) does not preclude the presence of gastric malignancy.
Since Ranitidine is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function caution should be observed in patients with hepatic dysfunction since Ranitidine is metabolized in the liver.
Rare reports suggest that Ranitidine may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Pregnancy:

Teratogenic Effects - Pregnancy Category B

Nursing Mothers:

Ranitidine is secreted in human milk. Caution should be exercised when Ranitidine is administered to a nursing mother.

Pediatric Use:

The safety and effectiveness of Ranitidine have been established in the age-group of 1 month to 16 years for the treatment of duodenal and gastric ulcers, gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed duodenal and gastric ulcer.

1.3.2.1d Clinical Pharmacology

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca^{++} in hypercalcemic states. Ranitidine is not an anticholinergic agent.

1.3.2.1d.1 Pharmacokinetics

Absorption:

Ranitidineis 50% absorbed after oral administration, compared to an intravenous (IV) injection with mean peak levels of 440 to 545 ng/mL occurring 2 to 3 hours after a 150-mg dose. Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of Ranitidine.

Distribution:

The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Metabolism:

In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to < 4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant, alterations in ranitidine half-life, distribution, clearance, and bioavailability.

Excretion:

The principal route of excretion is the urine, with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 410 mL/min, indicating active tubular excretion. The elimination half-life is 2.5 to 3 hours. Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance.

Geriatrics

The plasma half-life is prolonged and total clearance is reduced in the elderly population due to a decrease in renal function. The elimination half-life is 3 to 4 hours. Peak levels average 526 ng/mL following a 150-mg twice-daily dose and occur in about 3 hours .

Pediatrics

There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy adults when correction is made for body weight. The average bioavailability of ranitidine given orally to pediatric patients is 48% which is comparable to the bioavailability of ranitidine in the adult population. All other pharmacokinetic parameter values (t½, Vd, and CL) are similar to those observed with intravenous ranitidine use in pediatric patients.

Plasma clearance measured in 2 neonatal patients (less than 1 month of age) was considerably lower (3 mL/min/kg) than children or adults and is likely due to reduced renal function observed in this population.

1.3.2.1d.2 PHARMACODYNAMICS

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

1. *Effects on Acid Secretion:* Ranitidine inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin.
It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by Ranitidine, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. *Effects on Other Gastrointestinal Secretions: Pepsin:* Oral Ranitidine does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral Ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

1.3.2.1d.3 Other Pharmacologic Actions:

- Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
- Prolactin levels—no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.
- Other pituitary hormones—no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.
- No change in cortisol, aldosterone, androgen, or estrogen levels.

- No antiandrogenic action.
- No effect on count, motility, or morphology of sperm.[16]

1.3.2.2 Famotidine:

Famotidine is a histamine-2 blocker. It works by decreasing the amount of acid the stomach produces. Famotidine is used to treat and prevent ulcers in the stomach and intestines. It also treats conditions in which the stomach produces too much acid, such as Zollinger-Ellison syndrome. Famotidine also treats gastroesophageal reflux disease (GERD) and other conditions in which acid backs up from the stomach into the esophagus, causing heartburn.

1.3.2.2a Indication:

Short-term treatment of active duodenal ulcer:

Most adult patients heal within 4 weeks; there is rarely reason to use Famotidine at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulce:

Controlled studies in adults have not extended beyond one year.

Short-term treatment of active benign gastric ulce:

Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

Short-term treatment of gastroesophageal reflux disease (GERD):

Famotidine is indicated for short-term treatment of patients with symptoms of GERD. Famotidine is also indicated for the short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy.

Treatment of pathological hypersecretory conditions:

e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas

1.3.2.2b DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use Famotidine at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

Benign Gastric Ulcer

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD)

The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 or 40 mg b.i.d. for up to 12 weeks.

Peptic ulcer

0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations

1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some adult patients with severe Zollinger-Ellison Syndrome.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency

In adult patients with moderate (creatinine clearance < 50 mL/min) or severe (creatinine clearance < 10 mL/min) renal insufficiency, the elimination half-life of Famotidine is increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of Famotidine may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

Based on the comparison of pharmacokinetic parameters for Famotidine in adults and pediatric patients, dosage adjustment in pediatric patients with moderate or severe renal insufficiency should be considered.

Pregnancy: Pregnancy Category B

1.3.2.2c PHARMACOKINETICS

Famotidine is incompletely absorbed. The bioavailability of oral doses is 40-45%. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of Famotidine in plasma is protein bound. Famotidine has an elimination half-life of 2.5-3.5 hours. Famotidine is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of Famotidine. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, the elimination half-life of Famotidine may exceed 20 hours and adjustment of dose or dosing intervals in moderate and severe renal insufficiency may be necessary.

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of Famotidine. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased.

1.3.2.2d. PHARMACODYNAMICS

Gastrointestinal Effects

Famotidine is a competitive inhibitor of histamine H2-receptors. The primary clinically important pharmacological activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of basal, nocturnal and stimulated gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output. In normal volunteers and hypersecretors, famotidine inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, the onset of the anti-secretory effect occurred within one hour; the maximum effect was dose dependent, occurring within one to three hours. Duration of inhibition of secretion by doses of 20 and 40 mg was ten to twelve hours.[17]

1.3.3 PROTON PUMP INHIBITORS (PPIS)

Proton pump inhibitors (PPIs) are a class (group) of drugs that work on the cells that line the stomach, reducing the production of acid. They include: esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole, and come in various different brand names.

Proton pump inhibitors reduce the amount of acid made by your stomach. They are commonly used to treat acid reflux and ulcers of the stomach and duodenum. Most people who take a proton pump inhibitor do not develop any side effects.[18]

1.3.3a Use of PPIs

Proton pump inhibitors usually work very well to reduce stomach acid and to treat the above conditions. They have made a big impact on the quality of life of many people with these conditions since they first became available in the 1980s. They are commonly prescribed:

- ✓ To treat ulcers in the stomach and duodenum (part of the gut).

- ✓ To reduce acid reflux which may cause heartburn or oesophagitis (inflammation of the gullet).These conditions are sometimes called gastro-oesophageal reflux disease or GORD.
- ✓ As one part of treatment to get rid of Helicobacter pylori, a bacterium (germ) found in the stomach which can cause ulcers.
- ✓ To help prevent and treat ulcers associated with anti-inflammatory drugs called NSAIDs (non-steroidal anti-inflammatory drugs).
- ✓ In a rare condition called Zollinger-Ellison syndrome.
- ✓ In other conditions where it is helpful to reduce acid in the stomach. [19]

1.3.3b. Action of Proton pump inhibitors

Stomach normally produces acid to help with the digestion of food and to kill bacteria. This acid is corrosive so your body produces a natural mucus barrier which protects the lining of the stomach from being eroded.

In some people this barrier may have broken down allowing the acid to damage the stomach, causing an ulcer. In others there may be a problem with the muscular band at the top of the stomach (the sphincter) that keeps the stomach tightly closed. This may allow the acid to escape and irritate the oesophagus (gullet). This is called 'acid reflux' which can cause heartburn and/or oesophagitis.

PPIs stop cells in the lining of the stomach producing too much acid. This can help prevent ulcers from forming or assist the healing process. By decreasing the amount of acid they can also help to reduce acid reflux related symptoms such as heartburn.
They are called 'proton pump inhibitors' because they work by blocking (inhibiting) a chemical system called the hydrogen-potassium adenosine triphosphatase enzyme system (otherwise known as the 'proton pump'). This chemical system is found in the cells in the stomach lining that make stomach acid.[20]

1.3.3c quickly working of proton pump inhibitors

Generally, proton pump inhibitors are well absorbed by the body and may provide quick relief for some problems. For example, heartburn caused by acid reflux. However, if you are taking them for other reasons, such as to heal an ulcer, it may take longer for the drugs to have an underlying effect.

1.3.3d Treatment Period

This can vary depending on the reason you are taking a PPI. So, speak to your doctor for advice. For example, in some cases your doctor may prescribe a PPI that you only take 'as required' to relieve your symptoms, rather than every day. In some cases a regular dose taken each day is advised.

1.3.3e Patients for PPIs

PPIs may not be suitable for some people. For example, people with certain liver problems, or pregnant or breastfeeding mums. A full list of individuals who should not take a PPI is included with the information leaflet that comes in the drug packet. If you are prescribed or buy a PPI, read this to be sure you are safe to take it.

1.3.3f . Side-effects

Most people who take a PPI do not have any side effects. However, side effects occur in a small number of users. The most common side effects are:

- Constipation
- Diarrhoea
- Flatulence
- Headaches
- Nausea (feeling sick)
- Abdominal (tummy) pain
- Vomiting

Low magnesium levels in the body: This problem can be serious. Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months. If low magnesium levels happen, it is usually after a year of treatment. You may or may not have symptoms of low magnesium. Tell your doctor right away if you have any of these symptoms of low magnesium levels:

- seizures
- dizziness

- abnormal or fast heart beat, or skipped heartbeat
- jitteriness
- jerking movements or shaking (tremors)
- muscle weakness
- spasms of the hands and feet
- cramps or muscle aches
- spasm of the voice box

1.3.3g Other considerations when taking a proton pump inhibitor

- *Vomiting blood:* This may be obviously fresh blood, but altered blood in vomit can look like ground coffee. Doctors call this 'coffee-ground vomit'.
- *Blood in your stools (faeces):* This may be obvious blood, or it may just make your stools black.
- *Unintentional weight loss.*
- *Difficulty swallowing, including food getting stuck in the gullet.*
- *Persistent abdominal pain or persistent vomiting.*

1.3.3h Differences among proton pump inhibitors

Proton pump inhibitors are very similar in action and there is no evidence that one is more effective than another. They differ in how they are broken-down by the liver and their drug interactions. The effects of some PPIs may last longer and they, therefore, may be taken less frequently.

Dose varies with the indication. The following are commonly prescribed doses:

- Esomeprazole: 20 to 40 mg once a day.
- Lansoprazole: 15 to 30 mg once a day.
- Omeprazole: 20 to 40 mg once a day.
- Pantoprazole: 40 mg once or twice a day.
- Rabeprazole: 20 mg once a day. In hypersecretory conditions, doses as high as 60 mg twice daily have been reported.

In the above examples, the lower dose is usually adequate for GERD, while the higher dose may be required for ulcer therapy or hypersecretory conditions.

1.3.3i Interaction of proton pump inhibitors (PPIs)

Proton pump inhibitors interact with few drugs. The absorption into the body of some drugs is affected by the presence of acid in the stomach, and because PPIs reduce acid in the stomach, they may affect the absorption of these drugs. Specifically, PPIs reduce the absorption and concentration in the blood of ketoconazole and increase the absorption and concentration of digoxin. This may lead to reduced effectiveness of ketoconazole and an increase in digoxin toxicity.

Proton pump inhibitors can reduce the break-down of some drugs by the liver and lead to an increase in their concentration in the blood. Omeprazole (Prilosec) is more likely than the other PPIs to reduce the break-down of drugs by the liver. For example, omeprazole may increase the concentration in the blood of diazepam, warfarin and phenytoin.[21]

1.3.3j *History* of proton pump inhibitors

Evidence emerged by the end of the 1970s, that the newly discovered proton pump (H^+,K^+-ATPase) in the secretory membrane of the parietal cell was the final step in acid secretion. Literature from anaesthetic screenings, led attention to the potential antiviral compound pyridylthioacetamide which after further examination pointed the focus on an anti-secretory compound with unknown mechanisms of action called timoprazole. Timoprazole is a pyridylmethylsulfinyl benzimidazole and appealed due to its simple chemical structure and its surprisingly high level of anti-secretory activity.

Optimization of substituted benzimidazoles and their antisecretory effects where studied on the newly discovered proton pump to obtain higher pKa values of the pyridine, thereby facilitating accumulation within the parietal cell and increasing the rate of acid-mediated conversion to the active mediate. As a result of such optimization the first proton pump inhibiting drug was released on the market, omeprazole, a proton pump inhibitor (PPI) in 1979, and was the first of a new class of drug that control acid secretion in the stomach, a proton pump inhibitor (PPI). Addition of 5-methoxy-substitution to the benzimidazole moiety

of omeprazole was also made and gave the compound much more stability at neutral pH. In 1980, an Investigational New Drug (IND) application was filed and omeprazole was taken into Phase III human trials in 1982. A new approach for the treatment of acid-related diseases was introduced, and Omeprazole was quickly shown to be clinically superior to the histamine type-2 receptor antagonists, and was launced in 1988 as Losec® in Europe, and in 1990 as Prilosec® in the United States. In 1996, Losec® became the world's biggest ever selling pharmaceutical, and by 2004 over 800 million patients had been treated with the drug worldwide. During 1980s, about 40 other companies entered the PPIs area, but few achieved market success: Takeda with lansoprazole, Byk Gulden with pantoprazole, and Eisai with rabeprazole, all of which were analogues of omeprazole.

Other PPIs like lansoprazole and pantoprazole would follow in its footsteps, claiming their share of a flourishing market, after their own course of development. [22]

1.3.3k Basic structure

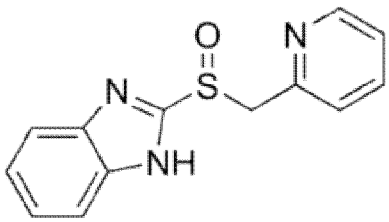


Fig 1.2: **Chemical structure of timoprazole, the backbone-structure of PPIs**

1.3.3l Clinical pharmacology of PPIs

Although these drugs omeprazole, lansoprazole, pantoprazole, and rabeprazole share common structure and mode of action, each differs somewhat in its clinical pharmacology. Differing pyridine and benzimidazole substituents result in small, but potentially significant different physical and chemical properties. Direct comparison of pantoprazole-sodium with other anti-secretory drugs showed that it was significantly more effective than H_2-receptor blockers and either equivalent or better than other clinically used PPIs. Another study states rabeprazole undergoes activation over a greater pH range than omeprazole, lansoprazole, and pantoprazole, and converts to the sulphenamide form more rapidly than any of these three drug. Most oral PPI preparations are enteric-coated, due to the rapid degradation of the drug

in the acidic conditions of the stomach. For example omeprazole is unstable in acid with a half-life of 2 min at pH 1-3, but is significantly more stable at pH 7 (half life ca. 20 h). The acid protective coating prevents conversion to the active principle in the lumen of the stomach, which then will react with any available sulfhydryl group in food and will not penetrate to the lumen of the secretory canaliculus

The oral bioavailability of PPIs is high; 77% for pantoprazole, 80-90% for lansoprazole and 89% for esomeprazole. All the PPIs except tenatoprazole are rapidly metabolized in the liver by CYP enzymes, mostly by CYP 2C19 and CYP 3A4. PPIs are sensitive to CYP enzymes and have different pharmacokinetic profiles. Studies comparing the efficacy of PPIs indicate that esomeprazole and tenatoprazole have stronger acid suppression, with a longer period of intragastric pH (pH > 4).

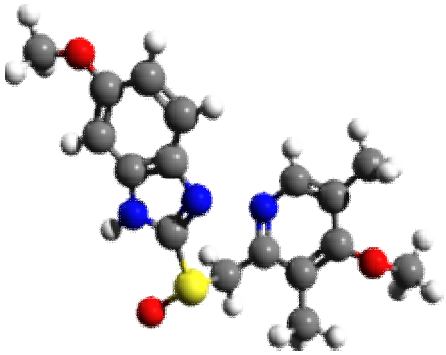
PPIs have been used successfully in triple-therapy regiments with clarithromycin and amoxicillin for the eradication of H.pylori with no significant difference between different PPI-based regimens.[23]

Table-1.7: Available Proton Pump Inhibitors (top brands) in Bangladesh

ANTIULCERANTS	Company	Dosage form	Value	Share	Growth
ACID PUMP INHIBITORS			9,502,102,463	78.56	37.71
OMEPRAZOLE			5,089,228,932	53.56	27.12
SECLO	Square	20 mg Capsule, 40 mg capsule, 40 mg IV Inj., 20 mg delayed release tablet, Powder Sachet	1,473,607,949	28.96	37.73
LOSECTIL	Skayef		934,741,054	18.37	26.46
XELDRIN	ACI		452,211,337	8.89	18.49
OMEP	Aristopharma		278,300,309	5.47	27.06
PPI	ACME		159,688,799	3.14	28.71
ESOMEPRAZOLE			2,260,894,212	23.79	57.49
MAXPRO	Renata	20 mg Capsule, 40 mg capsule, 40 mg	594,106,986	26.28	59.57
SERGEL	Healthcare		410,291,862	18.15	41.16

NEXUM	Square	IV Inj., 20 mg enteric coated tablet, 40 mg enteric coated tablet	195,156,907	8.63	52.29
ESONIX	Incepta		178,614,928	7.90	53.18
EXIUM	Radiant Pharma		123,040,136	5.44	86.89
PANTOPRAZOLE			1,412,973,928	14.87	39.82
PANTONIX	Incepta	20 mg Tablet & 40 mg Tablet, 40 mg IV Inj.	766,230,980	54.23	34.36
PANTOBEX	Beximco		175,313,005	12.41	83.10
PANTID	Opsonin		108,730,771	7.70	34.31
TRUPAN	Square		66,623,050	4.72	38.27
PANSEC	Drug International		51,626,597	3.65	22.69
RABEPRAZOLE			568,386,055	0.68	93.46
FINIX	Opsonin	20 mg Tablet	203,355,095	35.78	52.07
PARICEL	ACI		154,200,419	27.13	128.04
RABE	Aristopharma		123,445,542	21.72	234.73
RASONIX	Incepta		55,990,464	9.85	33.04
RABESEC	Drug International		18,221,131	3.21	61.46
ACIFIX	Beximco		7,188,636	1.26	999.00
LANSOPRAZOLE			170,619,336	0.20	8.93
LANSO	Square	30 mg Capsule	39,050,594	22.89	2.09
ZOTON	General		13,119,366	7.69	10.36
PROTOLAN	Beximco		5,774,583	3.38	6.43
LANSEC	Drug International		5,272,236	3.09	-30.49
LANSINA	Ibn Sina		4,916,746	2.88	40.55
LANSODIN	ACME		3,628,824	2.13	1.35

1.3.3.1 OMEPRAZOLE



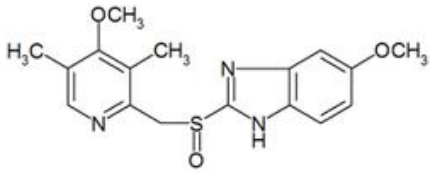


Fig 1.3 Omeprazole

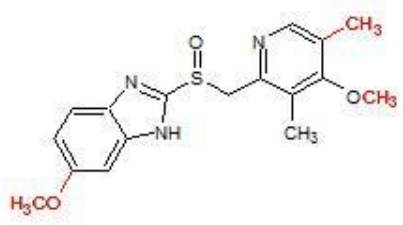


Fig 1.4 benzimidazoles

Omeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD), laryngopharyngeal reflux (LPR) and Zollinger-Ellison syndrome. Omeprazole is one of the most widely prescribed drugs internationally and is available over the counter in some countries.

Omeprazole was first marketed in the U.S. in 1989 by 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. It is now also available from generic manufacturers under various brand names.

AstraZeneca markets omeprazole as **Losec**, **Antra**, **Gastroloc**, **Mopral**, **Omepral**, and **Prilosec**. Omeprazole is marketed as **Zegerid** by Santarus, **Prilosec OTC** by Procter & Gamble and **Zegerid OTC** by Schering-Plough and as **Segazole** by Star Laboratories in Pakistan. In India it is available as **OMEZ** (Farhaad). In Bangladesh, it is made and marketed by Beacon Pharmaceuticals Ltd. under the brand name "**Xelopes**". **Xelopes** is also available as lyophilized injectable dosage form which was introduced in Bangladesh for the first time ever. Also Healthcare Pharmaceuticals Ltd. marketed omeprazole under the brand

name"**Opal**". **Opal** is available as 20 mg & 40 mg pellets in capsules. In Bangladesh **Apex Pharma Limited** also marketed omeprazole under the brand name **"Aspra"**. **Ozid** Capsule which manufactured by Pradja Pharin.

In 1990, at the request of the U.S. Food and Drug Administration (FDA), the brand name Losec was changed to Prilosec to avoid confusion with the diuretic Lasix (furosemide).

1.3.3.1a Indication:

Duodenal Ulcer (adults)

Omeprazole is indicated for short-term treatment of active duodenal ulcer in adults. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

Omeprazole in combination with clarithromycin and amoxicillin, is indicated for treatment of patients with H. pylori infection and duodenal ulcer disease (active or up to 1-year history) to eradicate H. pylori in adults.

Omeprazole in combination with clarithromycin is indicated for treatment of patients with H. pylori infection and duodenal ulcer disease to eradicate H. pylori in adults.

Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence

Among patients who fail therapy, Omeprazole with clarithromycin is more likely to be associated with the development of clarithromycin resistance as compared with triple therapy. In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Gastric Ulcer (adults)

Omeprazole is indicated for short-term treatment (4-8 weeks) of active benign gastric ulcer in adults.

Treatment of Gastroesophageal Reflux Disease (GERD) (adults and pediatric patients)

Symptomatic GERD

Omeprazole is indicated for the treatment of heartburn and other symptoms associated with GERD in pediatric patients and adults.

Erosive Esophagitis

Omeprazole is indicated for the short-term treatment (4-8 weeks) of erosive esophagitis that has been diagnosed by endoscopy in pediatric patients and adults.

The efficacy of Omeprazole used for longer than 8 weeks in these patients has not been established. If a patient does not respond to 8 weeks of treatment, an additional 4 weeks of treatment may be given. If there is recurrence of erosive esophagitis or GERD symptoms (eg, heartburn), additional 4-8 week courses of omeprazole may be considered.

Maintenance of Healing of Erosive Esophagitis (adults and pediatric patients)

Omeprazole is indicated to maintain healing of erosive esophagitis in pediatric patients and adults.

Pathological Hypersecretory Conditions (adults)

Omeprazole is indicated for the long-term treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis) in adults.

1.3.3.1b Dosage And Administration

Short-Term Treatment of Active Duodenal Ulcer

The recommended adult oral dose of Omeprazole is 20 mg once daily. Most patients heal within four weeks. Some patients may require an additional four weeks of therapy.

H. pylori Eradication for the Reduction of the Risk of Duodenal Ulcer Recurrence

Triple Therapy (Omeprazole /clarithromycin/amoxicillin)

The recommended adult oral regimen is Omeprazole 20 mg plus clarithromycin 500 mg plus amoxicillin 1000 mg each given twice daily for 10 days. In patients with an ulcer present at the time of initiation of therapy, an additional 18 days of Omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Dual Therapy (Omeprazole /clarithromycin)

The recommended adult oral regimen is Omeprazole 40 mg once daily plus clarithromycin 500 mg three times daily for 14 days. In patients with an ulcer present at the time of initiation of therapy, an additional 14 days of Omeprazole 20 mg once daily is recommended for ulcer healing and symptom relief.

Gastric Ulcer

The recommended adult oral dose is 40 mg once daily for 4-8 weeks.

Gastroesophageal Reflux Disease (GERD)

The recommended adult oral dose for the treatment of patients with symptomatic GERD and no esophageal lesions is 20 mg daily for up to 4 weeks. The recommended adult oral dose for the treatment of patients with erosive esophagitis and accompanying symptoms due to GERD is 20 mg daily for 4 to 8 weeks.

Maintenance of Healing of Erosive Esophagitis

The recommended adult oral dose is 20 mg daily.

Pathological Hypersecretory Conditions

The dosage of Omeprazole in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose is 60 mg once daily. Doses should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 120 mg three times daily have been administered. Daily dosages of greater than 80 mg should be administered in divided doses. Some patients with Zollinger-Ellison syndrome have been treated continuously with Omeprazole for more than 5 years.

Pediatric Patients

For the treatment of GERD and maintenance of healing of erosive esophagitis, the recommended daily dose for pediatric patients 1 to 16 years of age is as follows:

Patient Weight	Omeprazole Daily Dose
5 < 10 kg	5 mg
10 < 20 kg	10 mg
≥ 20 kg	20 mg

On a per kg basis, the doses of omeprazole required to heal erosive esophagitis in pediatric patients are greater than those for adults.

Alternative administrative options can be used for pediatric patients unable to swallow an intact capsule.

1.3.3.1c Adverse effects

Some of the most frequent side effects of omeprazole (experienced by over 1% of those taking the drug) are headache, diarrhea, abdominal pain, nausea, dizziness, trouble awakening and sleep deprivation, although in clinical trials the incidence of these effects with omeprazole was mostly comparable to that found with placebo. Other side effects may include iron and vitamin B12 deficiency, although there is very little evidence to support this.

1.3.3.1 d. Interactions

Omeprazole is a competitive inhibitor of the enzymes CYP2C19 and CYP2C9, and may therefore interact with drugs that depend on them for metabolism, such as diazepam, escitalopram, and warfarin; the concentrations of these drugs may increase if they are used concomitantly with omeprazole. Clopidogrel (Plavix) is an inactive prodrug that partially depends on CYP2C19 for conversion to its active form; inhibition of CYP2C19 blocks the activation of clopidogrel, thus reducing its effects and potentially increasing the risk of stroke

or heart attack in people taking clopidogrel to prevent these events. Omeprazole is also a competitive inhibitor of p-glycoprotein, as are other PPIs.

Drugs that depend on stomach pH for absorption may interact with omeprazole; drugs that depend on an acidic environment (such as ketoconazole or atazanavir) will be poorly absorbed, whereas acid-labile antibiotics (such as erythromycin) will be absorbed to a greater extent than normal due to the more alkaline environment of the stomach.

1.3.3.1e. Use In Specific Populations

Pregnancy: Pregnancy Category C

Reproductive studies in rats and rabbits with omeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are no adequate and well-controlled studies on the use of omeprazole in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. The vast majority of reported experience with omeprazole during human pregnancy is first trimester exposure and the duration of use is rarely specified, e.g., intermittent vs. chronic. An expert review of published data on experiences with omeprazole use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk .

Three epidemiological studies compared the frequency of congenital abnormalities among infants born to women who used omeprazole during pregnancy with the frequency of abnormalities among infants of women exposed to H2-receptor antagonists or other controls. A population-based prospective cohort epidemiological study from the Swedish Medical Birth Registry, covering approximately 99% of pregnancies, reported on 955 infants (824 exposed during the first trimester with 39 of these exposed beyond first trimester, and 131 exposed after the first trimester) whose mothers used omeprazole during pregnancy. In utero exposure to omeprazole was not associated with increased risk of any malformation (odds ratio 0.82, 95% CI 0.50-1.34), low birth weight or low Apgar score. The number of infants born with ventricular septal defects and the number of stillborn infants was slightly higher in

the omeprazole-exposed infants than the expected number in the normal population. The author concluded that both effects may be random.

A retrospective cohort study reported on 689 pregnant women exposed to either H2-blockers or omeprazole in the first trimester (134 exposed to omeprazole). The overall malformation rate was 4.4% (95% CI 3.6-5.3) and the malformation rate for first trimester exposure to omeprazole was 3.6% (95% CI 1.5-8.1). The relative risk of malformations associated with first trimester exposure to omeprazole compared with non-exposed women was 0.9 (95% CI 0.3-2.2). The study could effectively rule out a relative risk greater than 2.5 for all malformations. Rates of preterm delivery or growth retardation did not differ between the groups.

A controlled prospective observational study followed 113 women exposed to omeprazole during pregnancy (89% first trimester exposures). The reported rates of major congenital malformations was 4% for the omeprazole group, 2% for controls exposed to non-teratogens, and 2.8% in disease-paired controls (background incidence of major malformations 1-5%). Rates of spontaneous and elective abortions, preterm deliveries, gestational age at delivery, and mean birth weight did not differ between the groups. The sample size in this study has 80% power to detect a 5-fold increase in the rate of major malformation.

Several studies have reported no apparent adverse short-term effects on the infant when single dose oral or intravenous omeprazole was administered to over 200 pregnant women as premedication for cesarean section under general anesthesia.

Reproductive studies conducted with omeprazole on rats at oral doses up to 56 times the human dose and in rabbits at doses up to 56 times the human dose did not show any evidence of teratogenicity. In pregnant rabbits, omeprazole at doses about 5.5 to 56 times the human dose produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy loss. In rats treated with omeprazole at doses about 5.6 to 56 times the human dose, dose-related embryo/fetal toxicity and postnatal developmental toxicity occurred in offspring.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of a woman following oral administration of 20 mg. The peak concentration of omeprazole in breast milk was less than 7% of the peak serum concentration. This concentration would correspond to 0.004 mg of omeprazole in 200 mL of milk. Because omeprazole is excreted in human milk, because of the potential for serious adverse reactions in nursing infants from omeprazole, and because of the potential for tumorigenicity shown for omeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Use of Omeprazole in pediatric and adolescent patients 1 to 16 years of age for the treatment of GERD is supported by a) extrapolation of results, already included in the currently approved labeling, from adequate and well-controlled studies that supported the approval of Omeprazole for adults, and b) safety and pharmacokinetic studies performed in pediatric and adolescent patients. The safety and effectiveness of Omeprazole for the treatment of GERD in patients < 1 year of age have not been established. The safety and effectiveness of Omeprazole for other pediatric uses have not been established.

Geriatric Use

Omeprazole was administered to over 2000 elderly individuals (≥ 65 years of age) in clinical trials in the U.S. and Europe. There were no differences in safety and effectiveness between the elderly and younger subjects. Other reported clinical experience has not identified differences in response between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Pharmacokinetic studies have shown the elimination rate was somewhat decreased in the elderly and bioavailability was increased. The plasma clearance of omeprazole was 250 mL/min (about half that of young volunteers) and its plasma half-life averaged one hour, about twice that of young healthy volunteers. However, no dosage adjustment is necessary in the elderly.

Hepatic Impairment

Consider dose reduction, particularly for maintenance of healing of erosive esophagitis.

Renal Impairment

No dosage reduction is necessary.

Asian Population

Consider dose reduction, particularly for maintenance of healing of erosive esophagitis.

1.3.3.1f. Overdose

Reports have been received of overdosage with omeprazole in humans. Doses ranged up to 2400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, vomiting, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. Symptoms were transient, and no serious clinical outcome has been reported when PRILOSEC was taken alone. No specific antidote for omeprazole overdosage is known. Omeprazole is extensively protein bound and is, therefore, not readily dialyzable. In the event of overdosage, treatment should be symptomatic and supportive.

As with the management of any overdose, the possibility of multiple drug ingestion should be considered.

Single oral doses of omeprazole at 1350, 1339, and 1200 mg/kg were lethal to mice, rats, and dogs, respectively. Animals given these doses 16 showed sedation, ptosis, tremors, convulsions, and decreased activity, body temperature, and respiratory rate and increased depth of respiration.

1.3.3.1g. Clinical Pharmacology

1.3.3.1f.1Mechanism of Action

Omeprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

1.3.3.1g.2.Pharmacodynamics

Antisecretory Activity

After oral administration, the onset of the antisecretory effect of omeprazole occurs within one hour, with the maximum effect occurring within two hours. Inhibition of secretion is about 50% of maximum at 24 hours and the duration of inhibition lasts up to 72 hours. The antisecretory effect thus lasts far longer than would be expected from the very short (less than one hour) plasma half-life, apparently due to prolonged binding to the parietal H+/K+ ATPase enzyme. When the drug is discontinued, secretory activity returns gradually, over 3 to 5 days. The inhibitory effect of omeprazole on acid secretion increases with repeated once-daily dosing, reaching a plateau after four days.

Single daily oral doses of omeprazole ranging from a dose of 10 mg to 40 mg have produced 100% inhibition of 24-hour intragastric acidity in some patients.

Serum Gastric Effects

In studies involving more than 200 patients, serum gastrin levels increased during the first 1 to 2 weeks of once-daily administration of therapeutic doses of omeprazole in parallel with inhibition of acid secretion. No further increase in serum gastrin occurred with continued

treatment. In comparison with histamine H2-receptor antagonists, the median increases produced by 20 mg doses of omeprazole were higher (1.3 to 3.6 fold vs. 1.1 to 1.8 fold increase). Gastrin values returned to pretreatment levels, usually within 1 to 2 weeks after discontinuation of therapy.

Enterochromaffin-like (ECL) Cell Effects

Human gastric biopsy specimens have been obtained from more than 3000 patients treated with omeprazole in long-term clinical trials. The incidence of ECL cell hyperplasia in these studies increased with time; however, no case of ECL cell carcinoids, dysplasia, or neoplasia has been found in these patients. However, these studies are of insufficient duration and size to rule out the possible influence of long-term administration of omeprazole on the development of any premalignant or malignant conditions.

Other Effects

Systemic effects of omeprazole in the CNS, cardiovascular and respiratory systems have not been found to date. Omeprazole, given in oral doses of 30 or 40 mg for 2 to 4 weeks, had no effect on thyroid function, carbohydrate metabolism, or circulating levels of parathyroid hormone, cortisol, estradiol, testosterone, prolactin, cholecystokinin or secretin.

No effect on gastric emptying of the solid and liquid components of a test meal was demonstrated after a single dose of omeprazole 90 mg. In healthy subjects, a single I.V. dose of omeprazole (0.35 mg/kg) had no effect on intrinsic factor secretion. No systematic dose-dependent effect has been observed on basal or stimulated pepsin output in humans. However, when intragastric pH is maintained at 4.0 or above, basal pepsin output is low, and pepsin activity is decreased.

As do other agents that elevate intragastric pH, omeprazole administered for 14 days in healthy subjects produced a significant increase in the intragastric concentrations of viable bacteria. The pattern of the bacterial species was unchanged from that commonly found in saliva. All changes resolved within three days of stopping treatment.

The course of Barrett's esophagus in 106 patients was evaluated in a U.S. double-blind controlled study of Omeprazole 40 mg twice daily for 12 months followed by 20 mg twice

daily for 12 months or ranitidine 300 mg twice daily for 24 months. No clinically significant impact on Barrett's mucosa by antisecretory therapy was observed. Although neosquamous epithelium developed during antisecretory therapy, complete elimination of Barrett's mucosa was not achieved. No significant difference was observed between treatment groups in development of dysplasia in Barrett's mucosa and no patient developed esophageal carcinoma during treatment. No significant differences between treatment groups were observed in development of ECL cell hyperplasia, corpus atrophic gastritis, corpus intestinal metaplasia, or colon polyps exceeding 3 mm in diameter.

1.3.3.1g.3 Pharmacokinetics

Absorption

Omeprazole Delayed-Release Capsules contain an enteric-coated granule formulation of omeprazole (because omeprazole is acid-labile), so that absorption of omeprazole begins only after the granules leave the stomach. Absorption is rapid, with peak plasma levels of omeprazole occurring within 0.5 to 3.5 hours. Peak plasma concentrations of omeprazole and AUC are approximately proportional to doses up to 40 mg, but because of a saturable first-pass effect, a greater than linear response in peak plasma concentration and AUC occurs with doses greater than 40 mg. Absolute bioavailability (compared with intravenous administration) is about 30-40% at doses of 20-40 mg, due in large part to presystemic metabolism. In healthy subjects the plasma half-life is 0.5 to 1 hour, and the total body clearance is 500-600 mL/min.

Based on a relative bioavailability study, the AUC and Cmax of PRILOSEC (omeprazole magnesium) for Delayed-Release Oral Suspension were 87% and 88% of those for Omeprazole Delayed-Release Capsules, respectively.

The bioavailability of omeprazole increases slightly upon repeated administration of Omeprazole Delayed-Release Capsules.

Omeprazole Delayed-Release Capsule 40 mg was bioequivalent when administered with and without applesauce. However, Omeprazole Delayed-Release Capsule 20 mg was not bioequivalent when administered with and without applesauce. When administered with

applesauce, a mean 25% reduction in Cmax was observed without a significant change in AUC for Omeprazole Delayed-Release Capsule 20 mg. The clinical relevance of this finding is unknown.

Distribution

Protein binding is approximately 95%.

Metabolism

Omeprazole is extensively metabolized by the cytochrome P450 (CYP) enzyme system.

Excretion

Following single dose oral administration of a buffered solution of omeprazole, little if any unchanged drug was excreted in urine. The majority of the dose (about 77%) was eliminated in urine as at least six metabolites. Two were identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma — the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Combination Therapy with Antimicrobials

Omeprazole 40 mg daily was given in combination with clarithromycin 500 mg every 8 hours to healthy adult male subjects. The steady state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and T½ increases of 30%, 89% and 34% respectively) by the concomitant administration of clarithromycin. The observed increases in omeprazole plasma concentration were associated with the following pharmacological effects. The mean 24hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin.

The plasma levels of clarithromycin and 14-hydroxy-clarithromycin were increased by the concomitant administration of omeprazole. For clarithromycin, the mean Cmax was 10% greater, the mean Cmin was 27% greater, and the mean AUC0-8 was 15% greater when

clarithromycin was administered with omeprazole than when clarithromycin was administered alone. Similar results were seen for 14-hydroxy-clarithromycin, the mean Cmax was 45% greater, the mean Cmin was 57% greater, and the mean AUC0-8 was 45% greater. Clarithromycin concentrations in the gastric tissue and mucus were also increased by concomitant administration of omeprazole.

1.3.3.1 h. Dosage forms

Omeprazole 10 mg, From U.K.

Package of Losec (Omeprazole) 20 mg, purchased in Hong Kong

Omeprazole is available as tablets and capsules (containing omeprazole or omeprazole magnesium) in strengths of 10 mg, 20 mg, 40 mg, and in some markets 80 mg; and as a powder (omeprazole sodium) for intravenous injection. Most oral omeprazole preparations are enteric-coated, due to the rapid degradation of the drug in the acidic conditions of the

stomach. This is most commonly achieved by formulating enteric-coated granules within capsules, enteric-coated tablets, and the multiple-unit pellet system (MUPS).

It is also available for use in injectable form (I.V.) in Europe, but not in the U.S. The injection pack is a combination pack consisting of a vial and a separate ampule of reconstituting solution. Each 10 ml clear glass vial contains a white to off-white lyophilised powder consisting of omeprazole sodium 42.6 mg equivalent to 40 mg of omeprazole.

1.3.3.1 I. Multiple unit pellet system

Omeprazole tablets manufactured by AstraZeneca (notably Losec/Prilosec) are formulated as a "multiple unit pellet system" (MUPS). Essentially, the tablet consists of extremely small enteric-coated granules (pellets) of the omeprazole formulation inside an outer shell. When the tablet is immersed in an aqueous solution, as happens when the tablet reaches the stomach, water enters the tablet by osmosis. The contents swell from water absorption causing the shell to burst, releasing the enteric-coated granules. For most patients, the multiple-unit pellet system is of no advantage over conventional enteric-coated preparations. Patients for which the formulation is of benefit include those requiring nasogastric tube feeding and those with difficulty swallowing (dysphagia) because the tablets can be mixed with water ahead of time, releasing the granules into a slurry form, which is easier to pass down the feeding tube or to swallow than the pill.

1.3.3.1 J. Immediate release formulation

In June 2004 the FDA approved an immediate release preparation of omeprazole and sodium bicarbonate that does not require an enteric coating. This preparation employs sodium bicarbonate as a buffer to protect omeprazole from gastric acid degradation. This allows for the production of chewable tablets. This combination preparation is marketed in the United States by Santarus under the brand name **Zegerid**. Zegerid is marketed as capsules, chewable tablets, and powder for oral suspension. Zegerid is most useful for those patients who suffer from nocturnal acid breakthrough (NAB) or those patients who desire immediate relief. In India it is marketed by Dr. Reddy's Laboratories as powder formulation with the brand name **OMEZ-INSTA**. It is reported to have additional benefits with patients suffering from alcoholic gastritis and life-style associated gastritis.[24]

1.3.3.2. PANTOPRAZOLE

1.3.3.2a Development of Pantoprazole

The story of pantoprazoles discovery is a good example of the stepwise development of PPIs. The main focus of modification of the timoprazole was the benzimidazole part of its structure. Addition of a trifluoromethyl group to the benzimidazole moiety led to a series of very active compounds with varying solution-stability. In general fluoro substituents were found to block metabolism at the point where they were attached. Later the more balanced fluoroalkoxy substituent, instead of the highly lipophilic and strongly electron-withdrawing trifluoromethyl substituent, led to highly active compounds with supposed longer half-lives and higher solution stability.

It was realized that activity was somehow linked to instability in solution and then came to the conclusion that the cyclic sulfenamides, formed in acidic conditions, were the active principle of the PPIs. Finally, it was understood that seemingly small alterations in the backbone of timoprazole led nowhere, and focus had to be centered on the substituents on the backbone. However, necessary intramolecular rearrangement of the benzimidazole into sulfenamide posed severe geometric constraints. Optimal compounds would be those that were stable at neutral pH but were quikcly activated at low pH.

A clear-cut design of active inhibitors was still not possible because in the complex multi-step chemistry the influence of a substituent on each step in the cascade could be different, and therefore not predictable for the overall rate of the prerequisite acid activation. Smith Kline and French, which entered into collaboration with Byk Gulden mid-1984, greatly assisted in determining criteria for further development. From 1985, the aim was to identify a compound with good stability at neutral pH, sustaining this higher level of stability down to pH 5 but being rapidly activateable at lower pHs, combined with a high level of H^+/K^+-ATPase inhibition.

In 1986 pantoprazole sodium sesquihydrate was synthesized and from 1987 onwards the development of pantoprazole was switched to the sodium salt which is more stable and has better compatibility with other excipients used in the drug formulation.

Pantoprazole was identified after nearly seven years of research and registered for clinical use after a further seven years of development, and finally reached its first market in 1994 in Germany. During the course of the studies on pantoprazole, more than 650 PPIs had been synthesized and evaluated. Pantoprazole obtained high selection criteria in its development process – especially concerning the favorable low potential for interaction with other drugs. Good solubility of Pantoprazole and very high solution stability allowed it to become the first marketed PPI for intravenous use in critical care patients.

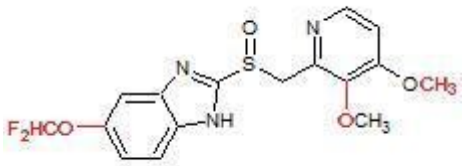


Fig 1.5: Pantoprazole.

Pantoprazole-sodium is available as gastroresistant or delayed release tablets and as lyophilized powder for intravenous use.

1.3.3.2b. Indications

Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

Pantoprazole is indicated in adults and pediatric patients five years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of Pantoprazole may be considered. Safety of treatment beyond 8 weeks in pediatric patients has not been established.

Maintenance of Healing of Erosive Esophagitis

Pantoprazole is indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

Pantoprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

1.3.3.2c. Dosage And Administration

Recommended Dosing Schedule

Pantoprazole is supplied as delayed-release granules in packets for preparation of oral suspensions or as delayed-release tablets. The recommended dosages -

Short-Term Treatment of Erosive Esophagitis Associated With GERD

Adults: 40 mg Once daily for up to 8 weeks

Children (5 years and older): ≥ 15 kg to < 40 kg: 20 mg once daily for up to 8 weeks

≥ 40 kg: 40 mg

Maintenance of Healing of Erosive Esophagitis

Adults: 40 mg Once daily

1.3.3.2d. Use In Specific Populations

Pregnancy - Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats at oral doses up to 88 times the recommended human dose and in rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to

pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use

The safety and effectiveness of Pantoprazole for short-term treatment (up to eight weeks) of erosive esophagitis (EE) associated with GERD have been established in pediatric patients 1 year through 16 years of age. Effectiveness for EE has not been demonstrated in patients less than 1 year of age. In addition, for patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, Pantoprazole is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of Pantoprazole for pediatric uses other than EE have not been established.

1 year through 16 years of age

Use of Pantoprazole in pediatric patients 1 year through 16 years of age for short-term treatment (up to eight weeks) of EE associated with GERD is supported by: a) extrapolation of results from adequate and well-controlled studies that supported the approval of Pantoprazole for treatment of EE associated with GERD in adults, and b) safety, effectiveness, and pharmacokinetic studies performed in pediatric patients.

Safety of Pantoprazole in the treatment of EE associated with GERD in pediatric patients 1 through 16 years of age was evaluated in three multicenter, randomized, double-blind,

parallel-treatment studies, involving 249 pediatric patients, including 8 with EE (4 patients ages 1 year to 5 years and 4 patients 5 years to 11 years). The children ages 1 year to 5 years with endoscopically diagnosed EE (defined as an endoscopic Hetzel-Dent score ≥ 2) were treated once daily for 8 weeks with one of two dose levels of Pantoprazole (approximating 0.6 mg/kg or 1.2 mg/kg). All 4 of these patients with EE were healed (Hetzel-Dent score of 0 or 1) at 8 weeks. Because EE is uncommon in the pediatric population, predominantly pediatric patients with endoscopically-proven or symptomatic GERD were also included in these studies. Patients were treated with a range of doses of Pantoprazole once daily for 8 weeks.

Neonates to less than one year of age

Pantoprazole was not found to be effective in a multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of 129 pediatric patients 1 through 11 months of age. Patients were enrolled if they had symptomatic GERD based on medical history and had not responded to non-pharmacologic interventions for GERD for two weeks. Patients received Pantoprazole daily for four weeks in an open-label phase, then patients were randomized in equal proportion to receive Pantoprazole treatment or placebo for the subsequent four weeks in a double-blind manner. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week treatment-withdrawal phase. There was no statistically significant difference between Pantoprazole and placebo in the rate of discontinuation.

In this trial, the adverse reactions that were reported more commonly (difference of ≥ 4%) in the treated population compared to the placebo population were elevated CK, otitis media, rhinitis, and laryngitis.

In a population pharmacokinetic analysis, the systemic exposure was higher in patients less than 1 year of age with GERD compared to adults who received a single 40 mg dose (geometric mean AUC was 103% higher in preterm infants and neonates receiving single dose of 2.5 mg of Pantoprazole, and 23% higher in infants 1 through 11 months of age receiving a single dose of approximately 1.2 mg/kg). In these patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 L/hr, range: 0.03 to 3.2 L/hr).

These doses resulted in pharmacodynamic effects on gastric but not esophageal pH. Following once daily dosing of 2.5 mg of PANTOPRAZOLE in preterm infants and neonates, there was an increase in the mean gastric pH (from 4.3 at baseline to 5.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 60% at baseline to 80% at steady-state). Following once daily dosing of approximately 1.2 mg/kg of PANTOPRAZOLE in infants 1 through 11 months of age, there was an increase in the mean gastric pH (from 3.1 at baseline to 4.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 32% at baseline to 60% at steady-state). However, no significant changes were observed in mean intraesophageal pH or % time that esophageal pH was < 4 in either age group.

Because Pantoprazole was not shown to be effective in the randomized, placebo-controlled study in this age group, the use of Pantoprazole for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

Geriatric Use

In short-term US clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with Pantoprazole were similar to those found in patients under the age of 65. The incidence rates of adverse reactions and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

Gender

Erosive esophagitis healing rates in the 221 women treated with PANTOPRAZOLE Delayed-Release Tablets in US clinical trials were similar to those found in men. In the 122 women treated long-term with Pantoprazole 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse reactions were also similar for men and women.

1.3.3.2e. Overdose

Experience in patients taking very high doses of Pantoprazole (> 240 mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile of Pantoprazole.

Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

1.3.3.2f. Clinical Pharmacology

1.3.3.2f.1. Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+, K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H+, K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

1.3.3.2f.2 Pharmacodynamics

Pantoprazole for Delayed-Release Oral Suspension, 40 mg has been shown to be comparable to Pantoprazole Delayed-Release Tablets in suppressing pentagastrin-stimulated MAO in patients (n = 49) with GERD and a history of EE. In this multicenter, pharmacodynamic crossover study, a 40 mg oral dose of Pantoprazole For Delayed-Release Oral Suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of Pantoprazole Delayed-Release Tablets after administration of each formulation once daily for

7 days. Both medications were administered thirty minutes before breakfast. Pentagastrin-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of intravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of PANTOPRAZOLE for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8-week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with PANTOPRAZOLE Delayed-Release Tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following short-term treatment with PANTOPRAZOLE, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density, starting after the first year of use, which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery.

1.3.3.2f.3 Pharmacokinetics

Pantoprazole Delayed-Release Tablets are prepared as enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (Cmax) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

In extensive metabolizers with normal liver function receiving an oral dose of the entericcoated 40 mg pantoprazole tablet, the peak concentration (Cmax) is 2.5 µg/mL; the time to reach the peak concentration (tmax) is 2.5 h, and the mean total area under the plasma

concentration versus time curve (AUC) is 4.8 µg•h/mL (range 1.4 to 13.3 µg•h/mL). Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h, and its apparent volume of distribution is 11.0-23.6 L.

Absorption

After administration of a single or multiple oral 40 mg doses of Pantoprazole Delayed-Release Tablets, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and Cmax was 2.5 µg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.

Administration of Pantoprazole Delayed-Release Tablets with food may delay its absorption up to 2 hours or longer; however, the Cmax and the extent of pantoprazole absorption (AUC) are not altered. Thus, PANTOPRAZOLE Delayed-Release Tablets may be taken without regard to timing of meals.

Administration of pantoprazole granules, 40 mg, with a high-fat meal delayed median time to peak plasma concentration by 2 hours. With a concomitant high-fat meal, the Cmax and AUC of pantoprazole granules, 40 mg, sprinkled on applesauce decreased by 51% and 29%, respectively. Thus, PANTOPRAZOLE For Delayed-Release Oral Suspension should be taken approximately 30 minutes before a meal.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent

sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Elimination

After a single oral or intravenous dose of 14C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

1.3.3.2f.4. Pharmacogenomics

CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10.0 hours in adults, they still have minimal accumulation ($\leq$ 23%) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed.

Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

For known pediatric poor metabolizers, a dose reduction should be considered.

1.3.3.2f.5. Animal Toxicology and/or Pharmacology

Studies in neonatal/juvenile and adult rats and dogs were performed. The data from these studies revealed that animals in both age groups respond to pantoprazole in a similar manner. Gastric alterations, including increased stomach weights, increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, were observed in the fundic mucosa of stomachs in repeated-dose studies. Decreases in red cell mass parameters, increases in cholesterol and triglycerides,

increased liver weight, enzyme induction, and hepatocellular hypertrophy were also seen in repeated-dose studies in rats and/or dogs. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

Reproductive Toxicology Studies

Reproduction studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.[25]

1.3.3.3 ESOMEPRAZOLE

Esomeprazole is a proton pump inhibitor (brand names **Zoleri**, **Esomeprazole**, **Lucen**, **Esopral**; **Axagon** in Italy, **Nexiam** in Belgium and South Africa; **Sompraz** and **Esomac** in India) developed and marketed by AstraZeneca which is used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD) and Zollinger-Ellison syndrome. Esomeprazole is the S-enantiomer of omeprazole (marketed as Losec/Prilosec), and AstraZeneca claims improved efficacy of this single enantiomer product over the racemic mixture of omeprazole. However, this greater efficacy has been disputed, with some claiming it offers no benefit from its older form.

Esomeprazole is a proton pump inhibitor which reduces acid secretion through inhibition of ATPase in gastric parietal cells. By inhibiting the functioning of this enzyme, the drug prevents formation of gastric acid.

Esomeprazole is the *S*-enantiomer of omeprazole and AstraZeneca (Parent company) claims improved efficacy of this single enantiomer product over the racemic mixture of omeprazole.

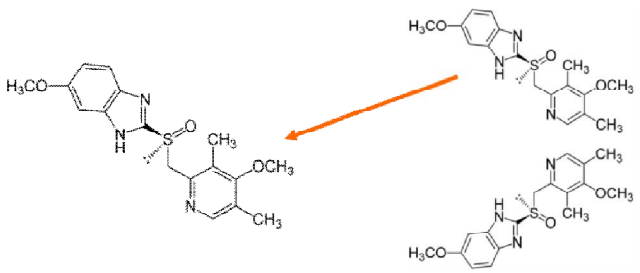


Fig 1.6: Esomeprazole

1.3.3.3a. Indications

Treatment of Gastroesophageal Reflux Disease (GERD)

Healing of Erosive Esophagitis

Esomeprazole is indicated for the short-term treatment (4 to 8 weeks) in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis. For those patients who have not healed after 4 to 8 weeks of treatment, an additional 4 to 8 week course of Esomeprazole may be considered.

In infants 1 month to less than 1 year, Esomeprazole is indicated for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD.

Maintenance of Healing of Erosive Esophagitis

Esomeprazole is indicated to maintain symptom resolution and healing of erosive esophagitis. Controlled studies do not extend beyond 6 months.

Symptomatic Gastroesophageal Reflux Disease

Esomeprazole is indicated for short-term treatment (4 to 8 weeks) of heartburn and other symptoms associated with gerd in adults and children 1 year or older.

Risk Reduction of NSAID-Associated Gastric Ulcer

Esomeprazole is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers. Patients are considered to be at risk due to their age ($\geq$ 60) and/or documented history of gastric ulcers. Controlled studies do not extend beyond 6 months.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy (Esomeprazole plus amoxicillin and clarithromycin): Esomeprazole, in combination with amoxicillin and clarithromycin, is indicated for the treatment of patients

with H. pylori infection and duodenal ulcer disease (active or history of within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome:

Esomeprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome.

1.3.3.3b Dosage & Administration:

Usual Adult Dose for Gastroesophageal Reflux Disease

20 mg orally once a day for 4 to 8 weeks. It may be administered by the intravenous route if unable to use oral route.

Usual Adult Dose for Erosive Esophagitis

Healing: 20 to 40 mg orally once a day for 4 to 8 weeks. It may be administered by the intravenous route if unable to use oral route.

Maintenance of healing: 20 mg orally once daily, for up to 6 months.

Usual Adult Dose for Helicobacter pylori Infection

40 mg orally once a day for 10 days along with amoxicillin 1000 mg and clarithromycin 500 mg orally twice a day for 10 days.

Usual Adult Dose for NSAID-Induced Gastric Ulcer

20 to 40 mg orally once daily for up to 6 months.

Usual Adult Dose for Zollinger-Ellison Syndrome

40 mg orally twice daily. Doses up to 240 mg daily have been used.

Usual Adult Dose for Pathological Hypersecretory Conditions

40 mg orally twice daily. Doses up to 240 mg daily have been used.

Usual Pediatric Dose for Gastroesophageal Reflux Disease

Short-term treatment:

1 to 11 years old: 10 mg orally once daily for up to 8 weeks.

12 to 17 years old: 20 mg to 40 mg orally once daily for up to 8 weeks.

When oral therapy is not possible or appropriate (GERD with Erosive Esophagitis):

1 month to less than 1 year of age: 0.5 mg/kg once daily IV over 10 minutes to 30 minutes.

1 year to 17 years: Body weight less than 55 kg: 10 mg once daily IV over 10 minutes to 30 minutes. Body weight 55 kg or greater: 20 mg once daily IV over 10 minutes to 30 minutes

Usual Pediatric Dose for Erosive Esophagitis

Healing: Less than 20 kg: 10 mg orally once daily for up to 8 weeks.

Greater than or equal to 20 kg: 10 mg to 20 mg orally once daily for up to 8 weeks.

Renal Dose Adjustments

No adjustments recommended

Liver Dose Adjustments

No dosage adjustment is recommended for patients with mild to moderate hepatic insufficiency (Child-Pugh class A and B). In patients with severe hepatic insufficiency (Child-Pugh class C), the maximum daily dose should not exceed 20 mg.

1.3.3.3c Evidence of efficacy

AstraZeneca claims that esomeprazole provides improved efficacy, in terms of stomach acid control, over the R enantiomer of omeprazole. Many health professionals have expressed the view that this improvement in efficacy is due to the dose of esomeprazole recommended for therapy rather than any inherent superiority of esomeprazole.

An alternative rationale suggested for the use of esomeprazole was the reduction in interindividual variability in efficacy. However the clinical advantage of this hypothesis has not thoroughly been tested in large-scale trials.

1.3.3.3d. Use In Specific Populations

Pregnancy

Pregnancy Category B

Reproductive studies in rats and rabbits with Esomeprazole and multiple cohort studies in pregnant women with omeprazole use during the first trimester do not show an increased risk of congenital anomalies or adverse pregnancy outcomes. There are, however, no adequate and well controlled studies of Esomeprazole use in pregnancy. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Esomeprazole is the s-isomer of omeprazole. In four population-based cohort studies that included 1226 women exposed during the first trimester of pregnancy to omeprazole there was no increased risk of congenital anomalies.

Nursing Mothers

Omeprazole concentrations have been measured in breast milk of one woman taking omeprazole 20 mg per day. However, the excretion of esomeprazole in milk has not been studied. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for Esomeprazole in rat carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The safety and effectiveness of Esomeprazole have been established in pediatric patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD. The safety and effectiveness of Esomeprazole have been established in pediatric patients 1 month to less than 1 year for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD. However, the safety and effectiveness of Esomeprazole have not been established in patients less than 1 month of age.

1 to 17 years of age

Use of Esomeprazole in pediatric and adolescent patients 1 to 17 years of age for short-term treatment (up to eight weeks) of GERD is supported by extrapolation of results from adequate and well-controlled studies for adults and safety and pharmacokinetic studies performed in pediatric and adolescent patients. The safety and effectiveness of Esomeprazole for other pediatric uses have not been established.

Erosive esophagitis due to acid-mediated GERD in infants 1 month to less than one year of age

Use of Esomeprazole in pediatric patients 1 month to less than 1 year of age for short-term treatment (up to 6 weeks) of erosive esophagitis due to acid-mediated GERD is supported by extrapolation of results from adequate and well-controlled studies for adults and safety, pharmacokinetic, and pharmacodynamic studies performed in pediatric patients .

Symptomatic GERD in infants 1 month to less than one year of age

There was no statistically significant difference between Esomeprazole and placebo in the rate of discontinuation due to symptom worsening in a multicenter, randomized, double-blind, controlled, treatment-withdrawal study of 98 patients ages 1 to 11 months, inclusive. Patients were enrolled if they had either a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Twenty of 98 enrolled patients underwent endoscopy, and 6 patients were found to have erosive esophagitis on endoscopy at baseline. All patients received Esomeprazole Delayed-Release Oral Suspension once daily during a two-week, open-label phase of the study.

Neonates 0 to 1 month of age

Following administration of oral ESOMEPRAZOLE in neonates the geometric mean (range) for the apparent clearance (CL/F) was 0.55 L/h/kg (0.25-1.6 L/h/kg). The safety and effectiveness of ESOMEPRAZOLE in neonates have not been established.

Geriatric Use

Total number of patients who received esomeprazole in clinical trials, 1459 were 65 to 74 years of age and 354 patients were ≥ 75 years of age.

no overall differences in safety and efficacy were observed between the elderly and younger individuals, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

1.3.3.3e. Overdose

A single oral dose of esomeprazole at 510 mg/kg (about 103 times the human dose on a body surface area basis), was lethal to rats. The major signs of acute toxicity were reduced motor activity, changes in respiratory frequency, tremor, ataxia, and intermittent clonic convulsions.

The symptoms described in connection with deliberate Esomeprazole overdose (limited experience of doses in excess of 240 mg/day) are transient. Single doses of 80 mg of esomeprazole were uneventful. Reports of overdosage with omeprazole in humans may also

be relevant. Doses ranged up to 2,400 mg (120 times the usual recommended clinical dose). Manifestations were variable, but included confusion, drowsiness, blurred vision, tachycardia, nausea, diaphoresis, flushing, headache, dry mouth, and other adverse reactions similar to those seen in normal clinical experience. No specific antidote for esomeprazole is known. Since esomeprazole is extensively protein bound, it is not expected to be removed by dialysis. In the event of over dosage, treatment should be symptomatic and supportive.

1.3.3.3f. Pharmacokinctics

Absorption

Esomeprazole Delayed-Release Capsules and Esomeprazole For Delayed-Release Oral Suspension contain a bioequivalent enteric-coated granule formulation of esomeprazole magnesium. Bioequivalency is based on a single dose (40 mg) study in 94 healthy male and female volunteers under fasting condition. After oral administration peak plasma levels (Cmaj) occur at approximately 1.5 hours (Tmax). The Cmax increases proportionally when the dose is increased, and there is a three-fold increase in the area under the plasma concentration-time curve (AUC) from 20 to 40 mg. At repeated once-daily dosing with 40 mg, the systemic bioavailability is approximately 90% compared to 64% after a single dose of 40 mg. The mean exposure (AUC) to esomeprazole increases from 4.32 μmol*hr/L on Day 1 to 11.2 μmol*hr/L on Day 5 after 40 mg once daily dosing.

The AUC after administration of a single 40 mg dose of Esomeprazole is decreased by 43% to 53% after food intake compared to fasting conditions. Esomeprazole should be taken at least one hour before meals.

Distribution

Esomeprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 2 to 20 μmol/L. The apparent volume of distribution at steady state in healthy volunteers is approximately 16 L.

Metabolism

Esomeprazole is extensively metabolized in the liver by the cytochrome P450 (CYP) enzyme system. The metabolites of esomeprazole lack antisecretory activity. The major part of

esomeprazole's metabolism is dependent upon the CYP 2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP 3A4 which forms the sulphone metabolite. CYP 2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15 to 20% of Asians lack CYP 2C19 and are termed Poor Metabolizers. At steady state, the ratio of AUC in Poor Metabolizers to AUC in the rest of the population (Extensive Metabolizers) is approximately 2.

Following administration of equimolar doses, the S- and R-isomers are metabolized differently by the liver, resulting in higher plasma levels of the S- than of the R-isomer.

Excretion

The plasma elimination half-life of esomeprazole is approximately 1 to 1.5 hours. Less than 1% of parent drug is excreted in the urine. Approximately 80% of an oral dose of esomeprazole is excreted as inactive metabolites in the urine, and the remainder is found as inactive metabolites in the feces.

1.3.3.3f.1. Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproductive studies have been performed in rats at oral doses up to 280 mg/kg/day (about 57 times the human dose on a body surface area basis) and in rabbits at oral doses up to 86 mg/kg/day (about 35 times the human dose on a body surface area basis) and have revealed no evidence of impaired fertility or harm to the fetus due to esomeprazole.

Reproductive studies conducted with omeprazole in rats at oral doses up to 138 mg/kg/day (about 56 times the human dose on a body surface area basis) and in rabbits at doses up to 69 mg/kg/day (about 56 times the human dose on a body surface area basis) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (about 5.5 to 56 times the human dose on a body surface area basis) produced dose-related increases in embryo-lethality, fetal resorptions, and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole at 13.8 to 138.0 mg/kg/day (about 5.6 to 56 times the human dose on a body surface area basis).

1.3.3.3g. Dosage forms

40 mg Esomeprazole brand esomeprazole capsules

Esomeprazole is available as delayed-release capsules in the United States or as delayed release tablets in Australia and Canada (containing esomeprazole magnesium) in strengths of 20 mg and 40 mg; and as esomeprazole sodium for intravenous injection/infusion. Oral esomeprazole preparations are enteric-coated, due to the rapid degradation of the drug in the acidic conditions of the stomach. This is achieved by formulating capsules using the multiple-unit pellet system.

1.3.3.3h. Multiple unit pellet system

Esomeprazole capsules are formulated as a "multiple unit pellet system" (MUPS). Essentially, the capsule consists of extremely small enteric-coated granules (pellets) of the esomeprazole formulation inside an outer shell. When the capsule is immersed in an aqueous solution, as happens when the capsule reaches the stomach, water enters the capsule by osmosis. The contents swell from water absorption causing the shell to burst, releasing the enteric-coated granules. For most patients, the multiple-unit pellet system is of no advantage over conventional enteric-coated preparations. Patients for which the formulation is of benefit include those requiring nasogastric tube feeding and those with difficulty swallowing (dysphagia).[26]

1.3.3.4 LANSOPRAZOLE

1.3.3.4a. Discovery

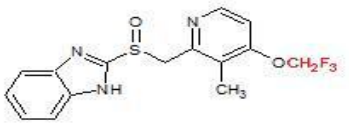


Fig 1.7: Lansoprazole.

Lansoprazole is a proton-pump inhibitor (PPI) which prevents the stomach from producing gastric acid. It is manufactured by a number of companies worldwide under several brand names (some brand names include: **Lansoprazole, Helicid, Zoton, Inhibitol, Monolitum**). It was first approved by the U.S. Food and Drug Administration (FDA) in 1995.

Lansoprazole patent protection expired on November 10, 2009. As a result, prescription Lansoprazole is now available in the form of a generic drug. As of November 12, 2009, Lansoprazole is available over-the-counter (OTC) in the U.S. in a 15 mg dose marketed by Novartis as **Lansoprazole 24HR**.

1.3.3.4b Indications

Short-Term Treatment of Active Duodenal Ulcer

Lansoprazole is indicated for short-term treatment (for 4 weeks) for healing and symptom relief of active duodenal ulcer.

H. pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Triple Therapy: Lansoprazole/amoxicillin/clarithromycin

Lansoprazole in combination with amoxicillin plus clarithromycin as triple therapy is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence [see Clinical Studies].

Dual Therapy: Lansoprazole/amoxicillin

Lansoprazole in combination with amoxicillin as dual therapy is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or one-year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

Maintenance of Healed Duodenal Ulcers

Lansoprazole is indicated to maintain healing of duodenal ulcers. Controlled studies do not extend beyond 12 months .

Short-Term Treatment of Active Benign Gastric Ulcer

Lansoprazole is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of active benign gastric ulcer [see Clinical Studies].

Healing of NSAID-Associated Gastric Ulcer

Lansoprazole is indicated for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use. Controlled studies did not extend beyond 8 weeks [see Clinical Studies].

Risk Reduction of NSAID-Associated Gastric Ulcer

Lansoprazole is indicated for reducing the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer who require the use of an NSAID. Controlled studies did not extend beyond 12 weeks.

Gastroesophageal Reflux Disease (GERD)

Short-Term Treatment of Symptomatic GERD

Lansoprazole is indicated for the treatment of heartburn and other symptoms associated with GERD.

Short-Term Treatment of Erosive Esophagitis

Lansoprazole is indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis. For patients who do not heal with Lansoprazole for 8 weeks (5 to 10%), it may be helpful to give an additional 8 weeks of treatment. If there is a recurrence of erosive esophagitis an additional 8-week course of Lansoprazole may be considered.

Maintenance of Healing of Erosive Esophagitis (EE)

Lansoprazole is indicated to maintain healing of erosive esophagitis. Controlled studies did not extend beyond 12 months.

Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (ZES)

Lansoprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

1.3.3.4c. Dosage and administration:

Usual Adult Dose for Erosive Esophagitis

Initial dose: 30 mg orally once a day for up to 8 weeks. Alternatively, if the patient is unable to use oral route the dose may be given as an IV infusion of 30 mg per day administered over 30 minutes for up to 7 days.

Maintenance dose: 15 mg orally once a day.

Usual Adult Dose for Duodenal Ulcer

15 mg orally once a day 30 minutes before eating. Therapy should be continued for up to 4 weeks.

Usual Adult Dose for Gastroesophageal Reflux Disease

15 mg orally once a day. Therapy should be continued for up to 8 weeks.

Usual Adult Dose for Gastric Ulcer

30 mg orally once a day 30 minutes before eating. Therapy should be continued for 4 to 8 weeks.

Usual Adult Dose for Multiple Endocrine Adenomas

60 mg orally once a day. Doses up to 90 mg orally 2 times a day have been used. The manufacturer reports that some patients have been treated continuously for as long as four years.

Usual Adult Dose for Systemic Mastocytosis

60 mg orally once a day. Doses up to 90 mg orally 2 times a day have been used. The manufacturer reports that some patients have been treated continuously for as long as four years.

Usual Adult Dose for Zollinger-Ellison Syndrome

60 mg orally once a day. Doses up to 90 mg orally 2 times a day have been used. The manufacturer reports that some patients have been treated continuously for as long as four years.

Usual Adult Dose for Helicobacter pylori Infection

Triple therapy: lansoprazole 30 mg is combined with 1 g of amoxicillin and 500 mg of clarithromycin given orally every 12 hours for 10 or 14 days. Most investigators recommend treatment with at least two antimicrobial agents in order to achieve eradication. Monotherapy with lansoprazole is ineffective and should be avoided.

Dual therapy: lansoprazole 30 mg is combined with 1 gram of amoxicillin given orally every 8 hours for 14 days. Refer to the monograph for amoxicillin and/or clarithromycin for dosing information specific to elderly or renally-impaired patients.

Usual Adult Dose for Duodenal Ulcer Prophylaxis

15 mg orally once a day 30 minutes before eating. Studies evaluating maintenance therapy for duodenal ulcers have not extended beyond 12 months.

Usual Adult Dose for NSAID-Induced Gastric Ulcer

30 mg orally once a day for 8 weeks.

Usual Adult Dose for NSAID-Induced Ulcer Prophylaxis

15 mg orally once a day for up to 12 weeks.

Usual Pediatric Dose for Aspiration Pneumonia

Greater than 3 to 11 years: 30 mg at night before surgery, and 30 mg at 5:30 a.m. the day of surgery.

Usual Pediatric Dose for Gastroesophageal Reflux Disease

Short term treatment of GERD (up to 12 weeks):

1 to 11 years: Less than or equal to 30 kg = 15 mg once daily, Greater than 30 kg = 30 mg once daily.

12 to 17 years: 15 mg once daily for up to 8 weeks

Usual Pediatric Dose for Erosive Esophagitis

Short term treatment (up to 12 weeks):

1 to 11 years: Less than or equal to 30 kg = 15 mg once daily

Greater than 30 kg = 30 mg once daily, up to 30 mg twice daily.

Short term treatment (up to 8 weeks):

12 to 17 years: 30 mg once daily

An additional 8 weeks may be tried in those patients who fail to respond or for a recurrence.

Maintenance: 15 mg once daily

Renal Dose Adjustments

No adjustments recommended

Liver Dose Adjustments

Erosive Esophagitis and Gastric Ulcer: 15 mg orally once a day.

Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas, and Systemic Mastocytosis: 30 mg orally once a day.

Helicobacter Pylori Infection: 15 mg orally twice a day.

Dose Adjustments

Daily doses above 120 mg should be administered in 2 equally divided doses.

1.3.3.4d. Mechanism of Action

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that suppress gastric acid secretion by specific inhibition of the (H+ , K +)-ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Lansoprazole does not exhibit anticholinergic or histamine type-2 antagonist activity.

1.3.3.4e. Pharmacokinetics

Lansoprazole Delayed-Release Capsules and Lansoprazole SoluTab Delayed-Release Orally Disintegrating Tablets contain an enteric-coated granule formulation of lansoprazole. Absorption of lansoprazole begins only after the granules leave the stomach. Absorption is rapid, with mean peak plasma levels of lansoprazole occurring after approximately 1.7 hours. After a single-dose administration of 15 mg to 60 mg of oral lansoprazole, the peak plasma concentrations (Cmax) of lansoprazole and the area under the plasma concentration curves

(AUCs) of lansoprazole were approximately proportional to the administered dose. Lansoprazole does not accumulate and its pharmacokinetics are unaltered by multiple dosing.

Absorption

The absorption of lansoprazole is rapid, with the mean Cmax occurring approximately 1.7 hours after oral dosing, and the absolute bioavailability is over 80%. In healthy subjects, the mean (±SD) plasma half-life was 1.5 (±1.0) hours. Both the Cmax and AUC are diminished by about 50% to 70% if lansoprazole is given 30 minutes after food, compared to the fasting condition. There is no significant food effect if lansoprazole is given before meals.

Distribution

Lansoprazole is 97% bound to plasma proteins. Plasma protein binding is constant over the concentration range of 0.05 to 5.0 mcg/mL.

Metabolism

Lansoprazole is extensively metabolized in the liver. Two metabolites have been identified in measurable quantities in plasma (the hydroxylated sulfinyl and sulfone derivatives of lansoprazole). These metabolites have very little or no antisecretory activity. Lansoprazole is thought to be transformed into two active species which inhibit acid secretion by blocking the proton pump [(H+, K+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. The two active species are not present in the systemic circulation. The plasma elimination half-life of lansoprazole is less than 2 hours while the acid inhibitory effect lasts more than 24 hours. Therefore, the plasma elimination half-life of lansoprazole does not reflect its duration of suppression of gastric acid secretion.

Elimination

Following single-dose oral administration of Lansoprazole, virtually no unchanged lansoprazole was excreted in the urine. In one study, after a single oral dose of 14C-lansoprazole, approximately one-third of the administered radiation was excreted in the urine and two-thirds was recovered in the feces. This implies a significant biliary excretion of the lansoprazole metabolites.

1.3.3.4f Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

Reproduction studies have been performed in pregnant rats at oral lansoprazole doses up to 150 mg/kg/day [40 times the recommended human dose (30 mg/day) based on body surface area (BSA)] and pregnant rabbits at oral lansoprazole doses up to 30 mg/kg/day (16 times the recommended human dose based on BSA) and have revealed no evidence of impaired fertility or harm to the fetus due to lansoprazole [27]

1.3.3.5 RABEPRAZOLE

1.3.3.5a Structure

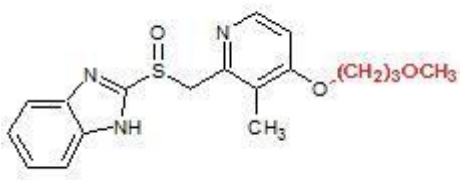


Fig 1.8 Rabeprazole

1.3.3.5b Discovery

Rabeprazole is a novel bensimidazole compound on market, since 1999 in USA. It is similar to lansoprazole in having no substituents on its bensimidazole part and a methyl group at site 3 on the pyridine, the only difference is the methoxypropoxy substitution at site 4 instead of the trifluoroethoxy group on lansoprazole. Rabeprazole is marketed as rabeprazole sodium salt. It is available as enteric-coated tablets.

Rabeprazole is an antiulcer drug in the class of proton pump inhibitors. It was developed by Eisai Co. and is marketed by Janssen-Cilag as rabeprazole sodium under the brand names Rabeprazole in the US and Pariet in Britain, Italy, Greece, Australia, Brazil, Canada, Japan, and Russia.

1.3.3.5c Indications

Healing of Erosive or Ulcerative GERD

Rabeprazole is indicated for short-term (4 to 8 weeks) treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of Rabeprazole may be considered.

Maintenance of Healing of Erosive or Ulcerative GERD

Rabeprazole is indicated for maintaining healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD Maintenance). Controlled studies do not extend beyond 12 months.

Treatment of Symptomatic GERD

Rabeprazole is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults and adolescents 12 years of age and above.

Healing of Duodenal Ulcers

Rabeprazole is indicated for short-term (up to four weeks) treatment in the healing and symptomatic relief of duodenal ulcers. Most patients heal within four weeks.

Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence

Rabeprazole in combination with amoxicillin and clarithromycin as a three drug regimen, is indicated for the treatment of patients with H. pylori infection and duodenal ulcer disease (active or history within the past 5 years) to eradicate H. pylori. Eradication of H. pylori has been shown to reduce the risk of duodenal ulcer recurrence.

In patients who fail therapy, susceptibility testing should be done. If resistance to clarithromycin is demonstrated or susceptibility testing is not possible, alternative antimicrobial therapy should be instituted.

Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

Rabeprazole is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

1.3.3.5d. Dosage & Administration:

Tablets should be swallowed whole and should not be crushed, split or chewed. Rabeprazole can be taken with or without meals since food has little effect on its absorption.

For healing ulcerating GERD, the recommended dose for adults is 20 mg daily for 4-8 weeks. If healing does not occur after 8 weeks, another 8 week course may be considered. The recommended maintenance dose is 20 mg daily.

Heartburn due to GERD is treated with 20 mg daily for 4 weeks and an additional 4 weeks if symptoms do not resolve.

Ulcers are treated with 20 mg daily for 4 weeks.

For the management of Zollinger-Ellison Syndrome, the starting dose for adults is 60 mg daily, and the dose is adjusted based on improvement in symptoms, healing of ulcers, or the effectiveness of acid suppression. Doses of 100 mg per day and 60 mg twice daily have been used in some patients with Zollinger-Ellison Syndrome.

The regimen for eradication of Helicobacter pylori is rabeprazole 20 mg, clarithromycin 500 mg, amoxicillin 1000 mg all given twice daily (morning and evening) for 7 days.

1.3.3.5e. Use In Specific Populations

Pregnancy

Teratogenic Effects. Pregnancy Category B: Teratology studies have been performed in rats at intravenous doses up to 50 mg/kg/day (plasma AUC of 11.8 µg•hr/mL, about 13 times the human exposure at the recommended dose for GERD) and rabbits at intravenous doses up to 30 mg/kg/day (plasma AUC of 7.3 µg•hr/mL, about 8 times the human exposure at the recommended dose for GERD) and have revealed no evidence of impaired fertility or harm to the fetus due to rabeprazole. There are, however, no adequate and well-controlled studies in

pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Following intravenous administration of 14C-labeled rabeprazole to lactating rats, radioactivity in milk reached levels that were 2- to 7-fold higher than levels in the blood. It is not known if unmetabolized rabeprazole is excreted in human breast milk. Administration of rabeprazole to rats in late gestation and during lactation at doses of 400 mg/kg/day (about 195-times the human dose based on mg/m2) resulted in decreases in body weight gain of the pups. Since many drugs are excreted in milk, and because of the potential for adverse reactions to nursing infants from rabeprazole, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Use of Rabeprazole in adolescent patients 12 years of age and above for short-term treatment of GERD is supported by a) extrapolation of results from adequate and well-controlled studies that supported the approval of Rabeprazole for adults; b) safety and pharmacokinetic studies performed in adolescent patients. The safety and effectiveness of Rabeprazole for the treatment of GERD patients < 12 years of age have not been established. The safety and effectiveness of Rabeprazole for other uses have not been established in pediatric patients.

In a multicenter, randomized, open-label, parallel-group study, 111 adolescent patients 12 to 16 years of age with a clinical diagnosis of symptomatic GERD or suspected or endoscopically proven GERD were randomized and treated with either Rabeprazole 10 mg or Rabeprazole 20 mg once daily for up to 8 weeks for the evaluation of safety and efficacy. The adverse event profile in adolescent patients was similar to that of adults. The related reported adverse reactions that occurred in ≥ 2% of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in these studies that were not previously observed in adults.

Geriatric Use: Of the total number of subjects in clinical studies of Rabeprazole, 19% were 65

years and over, while 4% were 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Gender

Duodenal ulcer and erosive esophagitis healing rates in women are similar to those in men. Adverse reactions and laboratory test abnormalities in women occurred at rates similar to those in men.

1.3.3.5f. Clinical Pharmacology

1.3.3.5f.1 Mechanism of Action

Rabeprazole belongs to a class of antisecretory compounds (substituted benzimidazole proton-pump inhibitors) that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but suppress gastric acid secretion by inhibiting the gastric H+, K+ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton-pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion.

In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide. When studied in vitro, rabeprazole is chemically activated at pH 1.2 with a half-life of 78 seconds. It inhibits acid transport in porcine gastric vesicles with a half-life of 90 seconds.

1.3.3.5f.2. Pharmacokinetics

Rabeprazole delayed-release tablets are enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. After oral administration of 20 mg Rabeprazole, peak plasma concentrations (Cmax) of rabeprazole occur over a range of 2.0 to 5.0 hours (Tmax). The rabeprazole Cmax and AUC are linear over an oral dose range of 10 mg to 40 mg. There is no appreciable accumulation when doses of 10 mg to 40 mg are

administered every 24 hours; the pharmacokinetics of rabeprazole is not altered by multiple dosing. The plasma half-life ranges from 1 to 2 hours.

Absorption

Absolute bioavailability for a 20 mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%. When rabeprazole is administered with a high fat meal, its Tmax is variable and may delay its absorption up to 4 hours or longer, however, the Cmax and the extent of rabeprazole absorption (AUC) are not significantly altered. Thus rabeprazole may be taken without regard to timing of meals.

Distribution

Rabeprazole is 96.3% bound to human plasma proteins.

Metabolism

Rabeprazole is extensively metabolized. A significant portion of rabeprazole is metabolized via systemic nonenzymatic reduction to a thioether compound. Rabeprazole is also metabolized to sulphone and desmethyl compounds via cytochrome P450 in the liver. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. In vitro studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3 to 5% of Caucasians and 17 to 20% of Asians). Rabeprazole metabolism is slow in these sub-populations, therefore, they are referred to as poor metabolizers of the drug.

Elimination

Following a single 20 mg oral dose of 14C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the dose was recovered in the feces. Total recovery of radioactivity was 99.8%. No unchanged rabeprazole was recovered in the urine or feces.[28]

Aims and Objectives

The objective of this study is to gain a better understanding of prescription pattern of Anti-ulcerants and the usage of these agents in different types of patients with different types of gastrointestinal disorders.

Significance of the study

Gastrointestinal acid-related diseases (ARDs) are very common problem in Bangladesh as well as in the World. According to 4P data (Product, Place, price & Promotion) from 4P Marketing Consultancy, Bangladesh, June, 2012 it is reported that 16.71% of patients are suffering from gastrointestinal acid related disorders. At past Antacids and H_2-blockers are widely used in treating of those diseases. Now-a-days proton pump inhibitors are very popular and widely prescribed for their better efficacy and safety profiles. Different types of PPIs are available in Bangladesh- Omeprazole, Esomeprazole, Pantoprazole, Rabeprazole, Lansoprazole. Each PPI is positioned in different type and group of patients. Our study will help to determine the usage of these agents in different types of patients with different types of gastrointestinal disorders. Significant of the study is to understand the prescription pattern and market situation of antiulcerants agents.

Chapter Two:

MATERIALS & METHODS

2.1 Topics of the study:

Prescription Pattern of Acid Suppressive Medications in Bangladesh

2.2 Objectives:

The objective of this study is to gain a better understanding of prescription pattern of Anti-ulcerants and the usage of these agents in different types of patients with different types of gastrointestinal disorders.

2.3 Study design:

The survey was conducted in 10 districts (Dhaka, Mymensingh, Comilla, Chittagong, Cox's Bazar, Bogra, Rangpur, Sylhet, Jessore) of 7 divisions of Bangladesh. Our target population is all Anti-ulcerants prescribers (especially Gastroenterologist, Medicine specialist, etc) from different health sectors of 10 districts. Our survey sample was drawn from this target population and the information or data was obtained from the sample once by questioning them and collecting the information provided by them. Papers of questionnaires about anti-ulcerant drugs were provided to target populations and information was collected for the completion of the survey.

2.4 Sample Selection:

Our target population is all Anti-ulcerants prescribers (especially Gastroenterologist, Medicine specialist, etc) from different health sectors of 10 districts. Our survey sample was drawn from this target population

2.5 Field work:

The survey data wascollected from 10 districts of Bangladesh from 4th February 2012 to 4th June 2012, which wasused for the development of study tools, collection of data and analysis

2.6 Data collection Method:

This paper consisted of multiple choice questions. An English language survey was developed based on information drawn from relevant literatures pertaining to rational use of anti-ulcerant drugs in health sectors of some developing countries. Questionnaires for physicians are covered their tendency to make anti-ulcerants

prescription in terms of frequency, disease severity, justification of the intravenous prescription at any given clinical condition and other relevant information.

Data also collected from 4P Marketing Consultancy June, 2012 and IMS 4Q, 2011.

2.7 Data analysis:

In this survey the statistical analysis wasperformed using MS Excel and Microsoft word 2007.

2.8 Question for Physician: *NB: The purpose of this survey is purely academic; confidentiality of information provided and anonymity of the respondents will be strictly maintained.*

INTERVIEWER **Name of the Physician:**

Name: **Specialization:**

Address: **Work place:**

ID#:

1. What type of anti-ulcerant you mostly choose for the treatment of **dyspepsia**?

a. Antacids b. Alginates (Mucosal protective agent) c. H_2 blocker
d. Proton Pump Inhibitor e. Others (Gastroprokinetics)

2. What type of anti-ulcerants you *mostly choose* in patients with symptoms of **gastroesophageal reflux disease** (GERD)?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d**. Concomitant therapy** with gastroprokinetic agents e.g. Domperidone, Metcloparamide, etc.

e. **Others** …… (Please write)

3. What type of different proton pump inhibitors you *mostly choose* in **preventing ulcer in patients taking nonsteroidal anti-inflammatory drugs**?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d. **Others** …….. (Please write)

4. What type of anti-ulcerant you *mostly choose* **in treating peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer**?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d. **Others.** …….. (Please write)

5. What type of proton pump inhibitors in preventing ulcer you *mostly choose* in triple therapy **to eradicate *Helicobacter pylori* infection**?

a. Omeprazole b. Esomeprazole c. Pantoprazole d. lansoprazole e. Rabeprazole

6. What type of anti-ulcerant you *mostly choose* in hypersecretory condition: **Zollinger-Ellison syndrome**?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d. **Others** …….. (Please write)

7. What you frequently do for **long term treatment** longer than 8 weeks in patients with gastroesophageal reflux disease or peptic ulcer?

a. Prescribing of higher dose of proton pump inhibitors compared with standard dose
b. stepping down to a lower dose of proton pump inhibitors, treatment as needed compared with daily treatment
c. Switching to an H_2 antagonist
d. Others …….. (Please write)

8. What types of anti-ulcerant you *mostly choose* for **pregnant women** in acid related disorder?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d. **Others.** …….. (Please write)

9. What type of anti-ulcerant you *mostly choose* for **geriatric patients** in acid related disorder?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. Lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d. **Others …**…….. (Please write)

10. What type of anti-ulcerant you *mostly choose* for **pediatric patients** in acid related disorder?

a. **Proton Pump Inhibitor:** 1. Omeprazole 2. Esomeprazole 3. Pantoprazole 4. lansoprazole 5. Rabeprazole

b. **H_2 blocker:** 1. Ranitidin 2.Famotidine 3.Roxatidine 4. Others

c. **Antacids**

d. **Others** …….. (Please write)

11. What types of Parenteral anti-ulcerant (Injection) you *mostly choose* **in prevention of acid aspiration syndrome during induction of surgical anaesthesia**?

a. Omeprazole injection b. Esomeprazole injection c. Pantoprazole injection
d. Ranitidine injection e. Others

12. What types of Parenteral anti-ulcerant (Injection) you *mostly choose* in patient with **severe hyperacidic conditions or patients who are unable to take oral therapy?**

a. Omeprazole injection b. Esomeprazole injection c. Pantoprazole injection
d. Ranitidine injection e. Others

Chapter Three:

RESULT & STATISTICAL ANALYSIS

3.1 Statistical analysis of data from interview

3.1.1 Type of anti-ulcerant mostly chosen for the treatment of dyspepsia

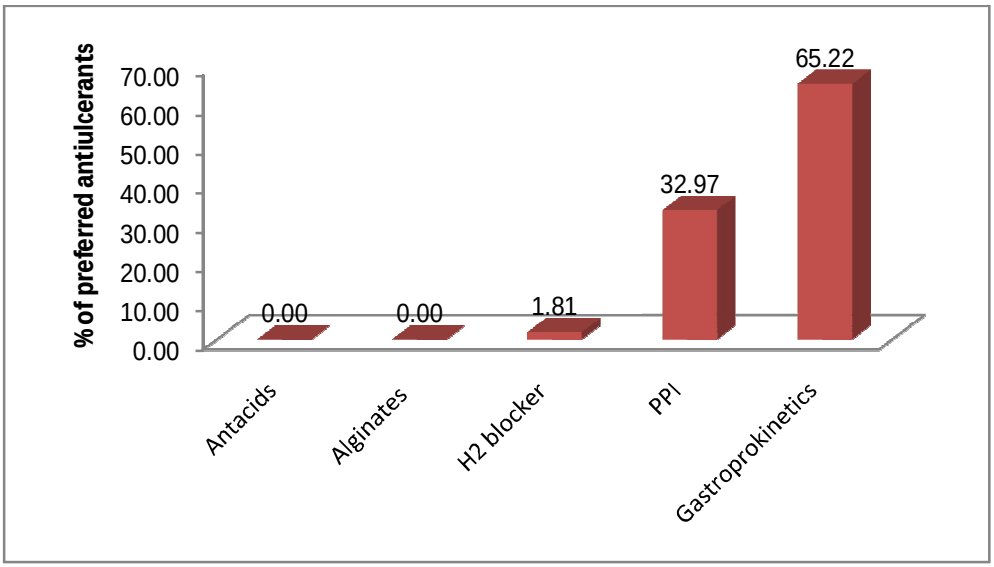


Figure-3.1: Preffered treatment option for dyspepsia

According to figure, prescribers mostly chose gastroprokinetics as domperidone for dyspepsia, and then second choice is Proton pump inhibitors.

Domperidone is an ideal gastroprokinetics drug, which enhances the motility of gut. It improves the rhythm of motility as well as maintains the contraction of intestine without disrupting its frequency. Domperidone is very safe drug for its minimum penetration through blood brain barrier. Thus domperidone is the choice of treatment for indigestion, gastroparesis, dyspepsia, etc.

3.1.2. Anti-ulcerants of choice by physicians in patients with symptoms of gastroesophageal reflux disease (GERD)

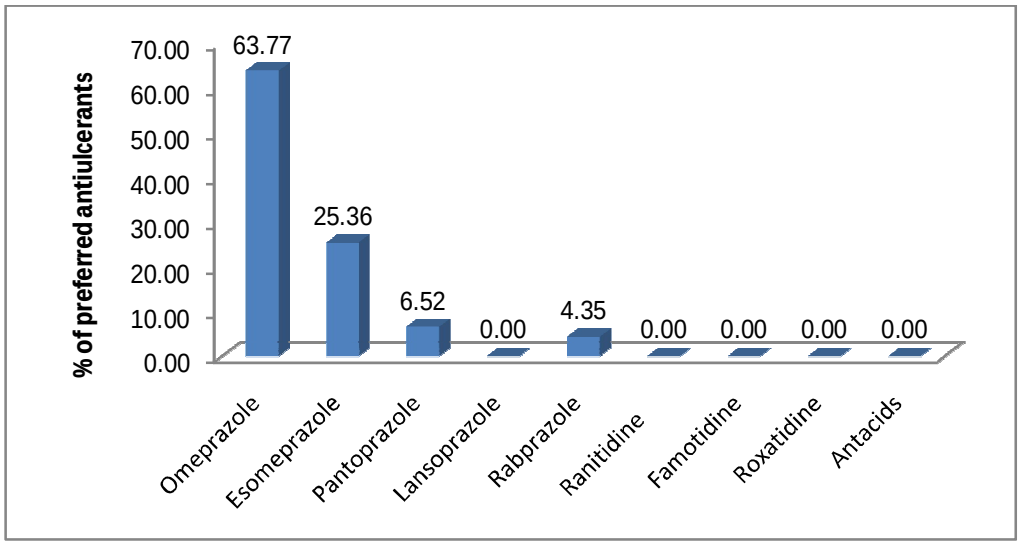


Fig-3.2:Antiulcerant for GERD

According to statistical analysis, we can found that most of the physicians choose Proton pump inhibitors for the treatment of GERD. Among the PPIs, Omeprazole is mostly chosen as 63.77 %. Then the second position is Esomeprazole, third is Pantoprazole and forth is Rabeprazole.

About 70% of GERD patients need long term therapy. As Omeprazole is safe for long term treatment (up to 11 years), it is mostly preferred by the physicians.

Esomeprazole maintains intra-gastric pH greater than 4 for longer periods. It is very effective and safe for maintaining gastric pH, so Esomeprazole is also prescribed in GERD frequently.

3.1.3. Anti-ulcerant for preventing ulcer in patients taking a nonsteroidal anti-inflammatory drug

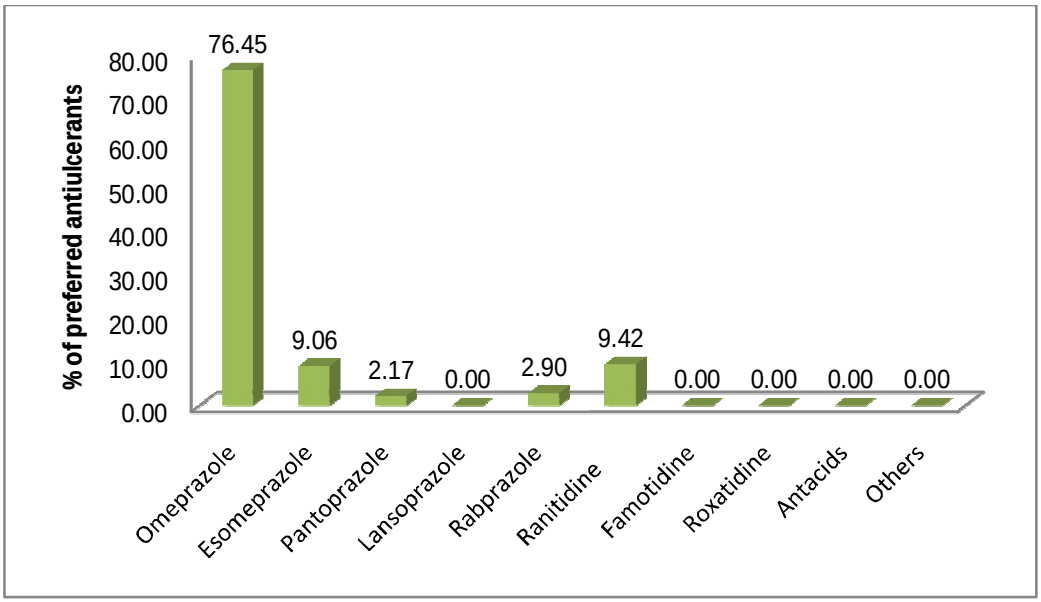


Fig.-3.3 Antiulcerants with NSAIDs

According to statistical analysis, we can found that most of the prescribers choose Proton pump inhibitors in preventing ulcer in patients taking a nonsteroidal anti-inflammatory drug. Among the PPIs, Omeprazole is mostly chosen as 76.45 %. Then the second position is Ranitidine, third Esomenprazole.

Omeprazole is first generic drug among all PPIs. It is a time tested & time trusted antiulcerant. USFDA approved Omeprazole as OTC product for treatment of Heart-burn

3.1.4. Anti-ulcerant in treating peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer

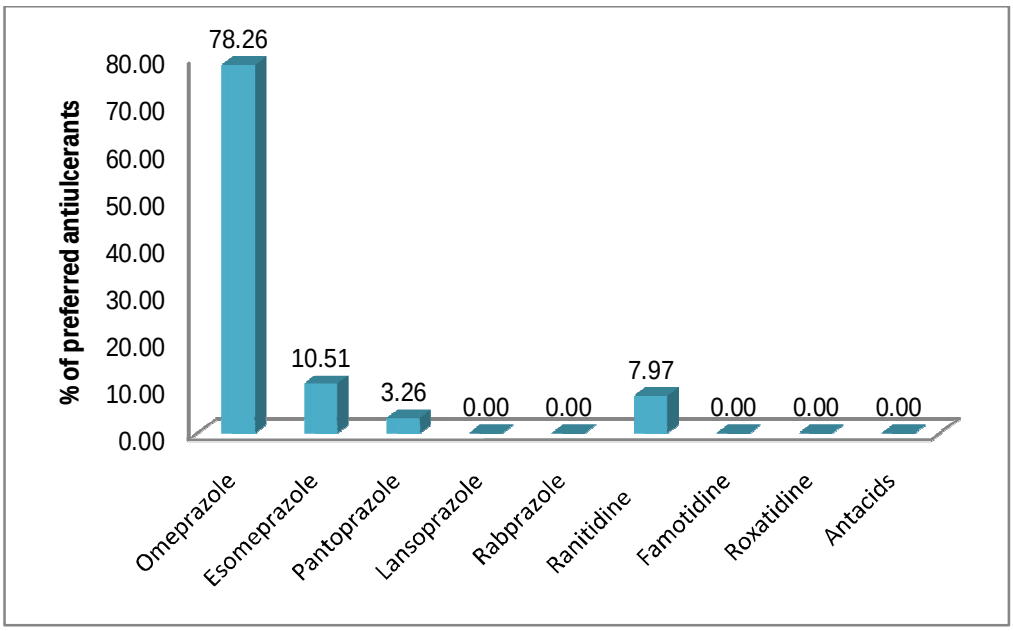


Fig.-3.4 Antiulcerants with NSAIDs

According to statistical analysis, we can found that most of the Prescribers chose Proton pump inhibitors in treating peptic ulcer and nonsteroidal anti-inflammatory drug-induced ulcer. Among the PPIs, Omeprazole is mostly chosen as 78.26 %. Then the second position is Esomenprazole & third is Ranitidine.

Omeprazole is first generic drug among all PPIs. It is a time tested & time trusted antiulcerant. USFDA approved Omeprazole as OTC product for treatment of Heart-burn.

Now-a-days Esomeprazole is most prescribed proton pump inhibitors in the world. It has least side effects among all proton pump inhibitors.

3.1.5. Proton pump inhibitors in preventing ulcer in triple therapy to eradicate Helicobacter pylori infection

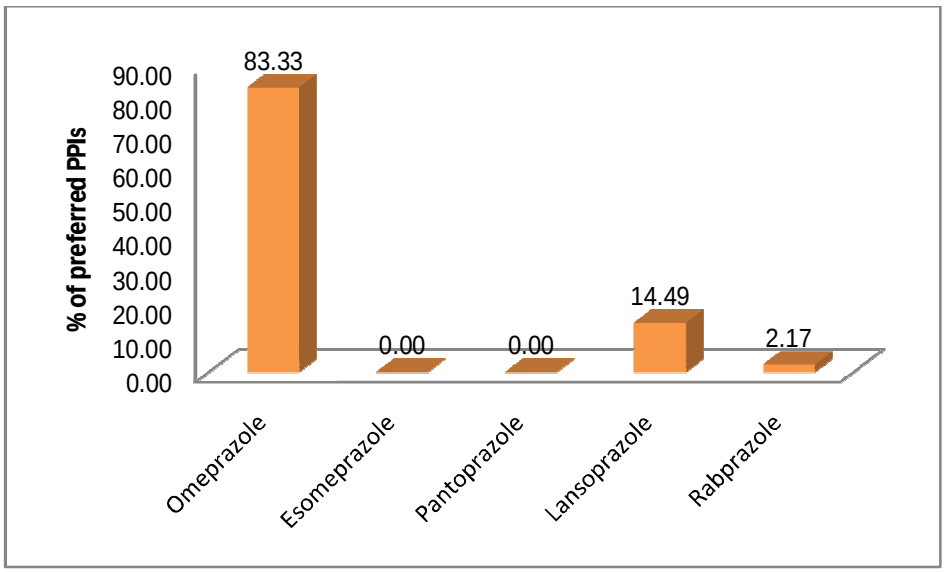


Fig.-3.5 Antiulcerants in *H.Pylori* positive PUD

According to statistical analysis, we can found that most of the physicians choose Omeprazole in triple therapy to eradicate Helicobacter pylori infection. Among the PPIs, then Lansoprazole and Rabeprazole are also prescribed**.**

Helicobacter pylori is an important cause of peptic ulcers. Greater than 90% of duodenal ulcer and 70% of gastric ulcers are associated with *H.Pylori.*

Traditional therapies are

Omeprazole 20 mg b.d. +Metronidazole 400 mg b.d. +Clarithromycin 500 mg b.d.

Lansoprazole 30 mg b.d. +Amoxycilin 500 mg b.d. +Clarithromycin 1 gm b.d.

Lansoprazole 30 mg b.d. +Amoxycilin 1000 mg b.d. +Clarithromycin 500 mg b.d.

3.1.6. Anti-ulcerants in hypersecretory condition: Zollinger-Ellison syndrome

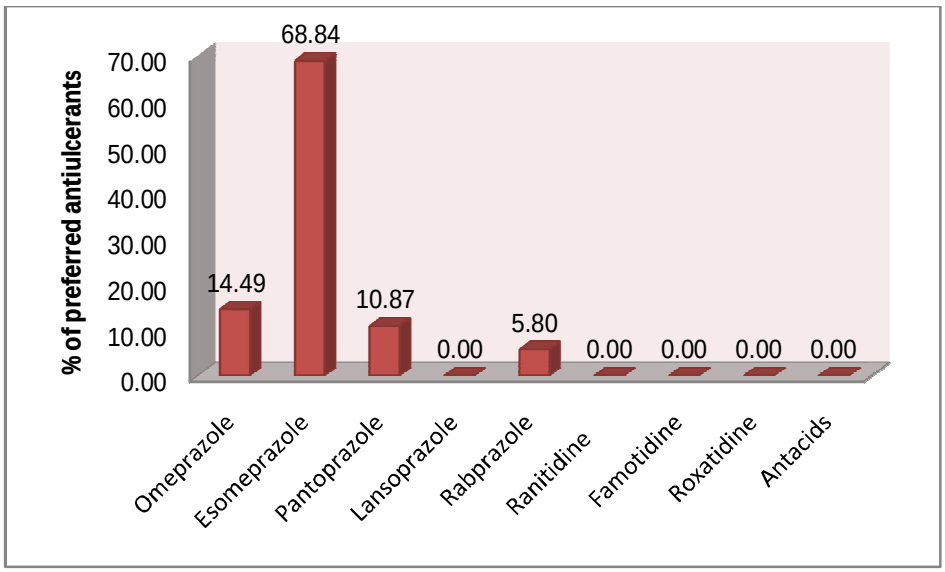


Fig.-3.6 Antiulcerants in hypersecretory conditions

According to statistical analysis, we can found that most of the prescribers choose proton pump inhibitors in hypersecretory condition: Zollinger-Ellison syndrome. Among the PPIs, Esomeprazole is mostly preferred as 68.84 %. Then Omeprazole is in second position, Pantoprazole is in third position and Ranitidine is in forth position**.**

Esomeprazole is superior in maintaining intragastric pH> 4.0. It has rapid onset of action. In some cases doctors prescribe higher strength of Esomeprazole. Clinical researchers have confirmed that Esomeprazole 40 mg once daily provides more effective control of gastric acid than standard doses of Lansoprazole, Omeprazole, Pantoprazole & Rabeprazole in GERD.

3.1.7. For long term treatment longer than 8 weeks in patients with gastroesophageal reflux disease or peptic ulcer

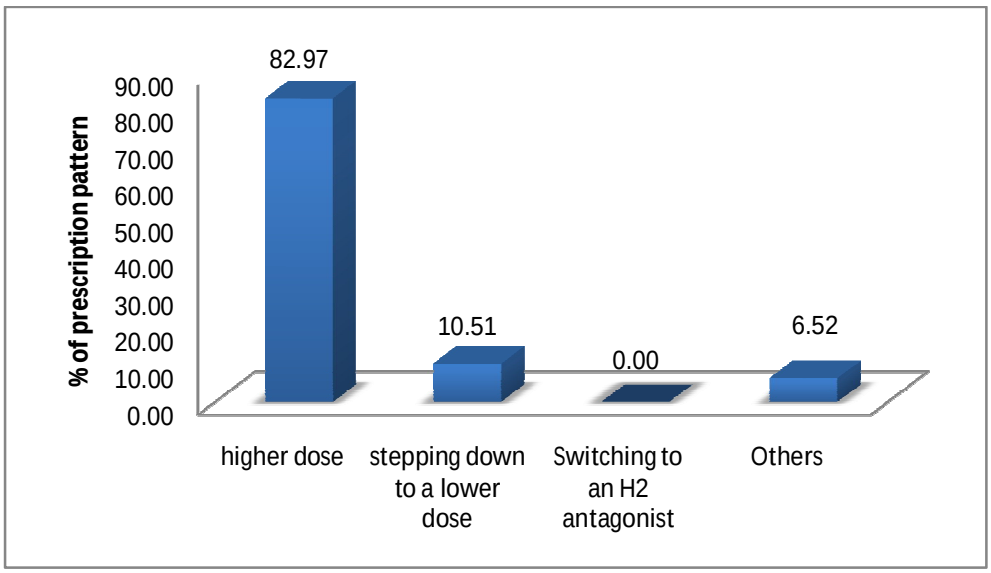


Fig.-3.6 preferred treatment option for long term treatment

According to statistical analysis, we can found that 82 % of prescribers preferred in Prescribing of higher dose of proton pump inhibitors compared with standard dose for long term treatment longer than 8 weeks in patients with gastroesophageal reflux disease or peptic ulcer. 10.51% of prescribers choose stepping down to a lower dose of proton pump inhibitors, treatment as needed compared with daily treatment for proton pump inhibitors for long term treatment longer than 8 weeks.

Esomeprazole 40 mg is prescribed for healing of erosive esophagitis, then Esomeprazole 20 is continues for maintaining healed erosive esophagitis.

In other cases initially patients are treated with standard dose, when they are not responded, then physicians prescribe higher dose of proton pump inhibitors.

3.1.8. Anti-ulcerant for pregnant women in acid related disorder

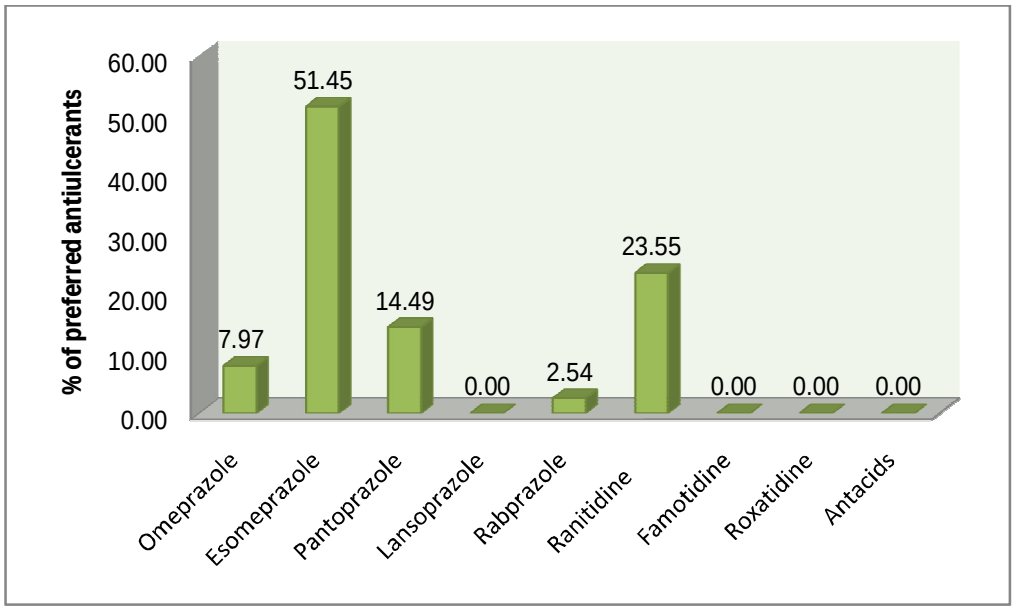


Fig.-3.8 preferred antiulcerants for pregnant women

According to statistical analysis, we can found that 51.45 % of prescribers preferred Esomeprazole as its pregnancy category is B, then Ranitidine 23.55%. Pantoprazole is in third position.

Esomeprazole USFDA approved pregnancy category is B. It has very least side effects.

Ranitidine USFDA approved pregnancy category is B. It is a time tasted H2 blocker. Still is preferred for its proven efficacy and safety profiles.

Now-a-days pantoprazole is positioning for pregnant women as its USFDA approved pregnancy category is B. Clinical studies found no significant harmful effect to the fetus or mother. No report was found in terms of teratogenic or infectious anomalies in fetus.

3.1.9. Antiulcerant for geriatric patients in acid related disorder.

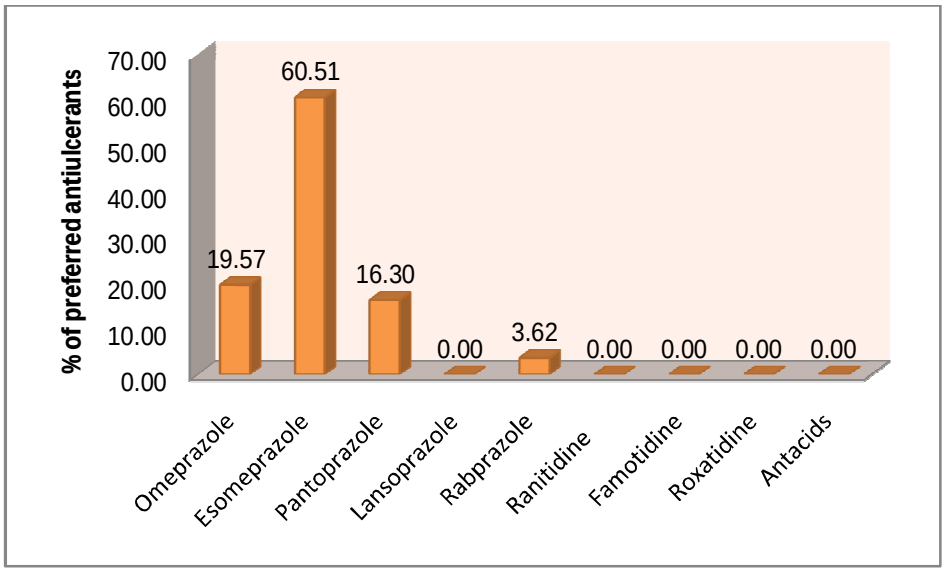


Fig.-3.9 preferred antiulcerants for geriatric patients

According to statistical analysis, we can found that 60.51 % of prescribers preferred Esomeprazole for it's highly safety profile. Then Omeprazole, Pantoprazole are also preferred by prescribers.

Esomeprazole is safe for all age group of patients. No dosage adjustment is needed for Esomeprazole in elderly patients, or renal or hepatic failure patients.

Omeprazole and pantoprazole is safe for long term treatment. So they are also preferred by physicians.

3.1.10. Anti-ulcerant for pediatric patients in acid related disorder

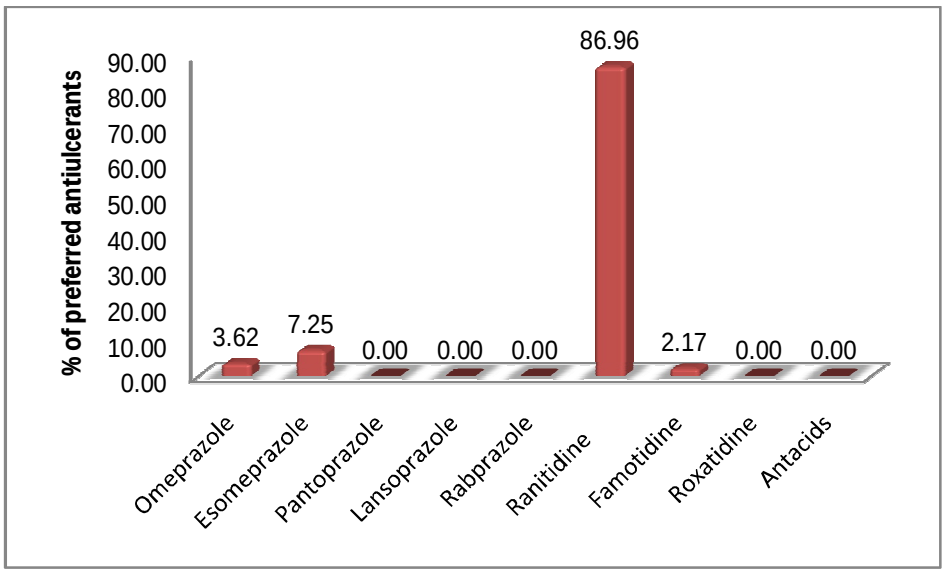


Fig.-3.10 preferred antiulcerants for geriatric patients

According to statistical analysis, we can found that 86.96 % of prescribers preferred Ranitidine for children. Then Esomeprazole, Omeprazole are also prescribed hardly.

In Bangladesh Ranitidine 75 mg/5 ml syrup is available. For the dosage convenience it is still popular for child patients. Then Omeprazole sachet powder is available. USFDA approved Esomeprazole for use in children from 1 year.

3.1.11. Parenteral anti-ulcerant (Injection) in prevention of acid aspiration syndrome during induction of surgical anesthesia

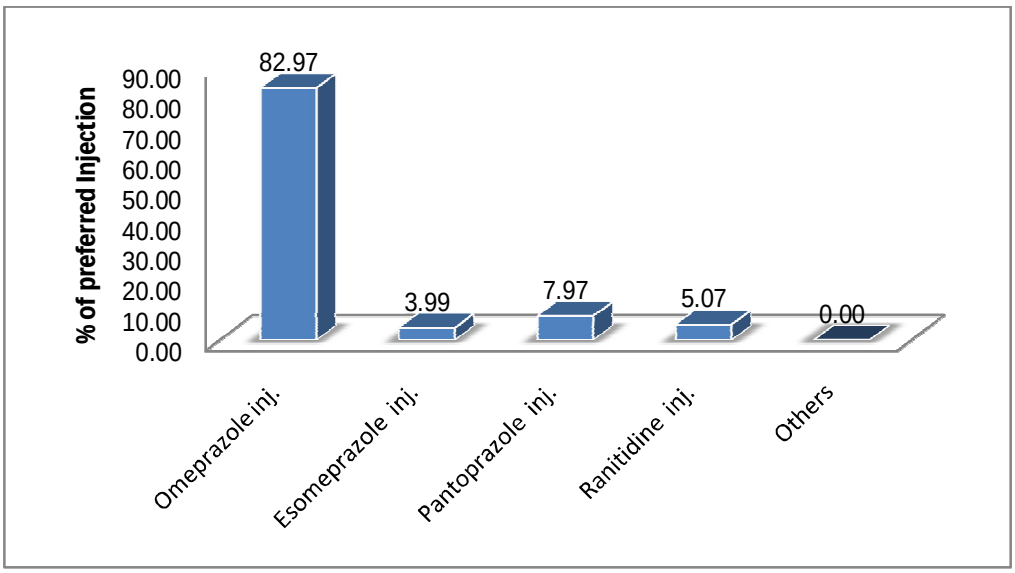


Fig.-3.11 preferred parenteral anti-ulcerant during induction of surgical anesthesia

According to statistical analysis, we can found that 82.97 % of prescribers preferred Omeprazole injection in prevention of acid aspiration syndrome during induction of surgical anesthesia. Then Esomeprazole, Pantoprazole and Ranitidine injection are also preferred.

The inhalation of oropharyngeal or gastric contents into the lower respiratory tract defines acid aspiration. In addition to anesthesia, gastroesophageal reflux disease is a prevalent risk factor for aspiration.

Omeprazole, the most widely prescribed & trusted Proton Pump Inhibitor. Omeprazole injection is highly effective severe hyperacidic condition and in prophylaxis of acid aspiration. Intravenous administration of Omeprazole 1 hour before the surgery produced- Greater gastric pH & smaller volume of gastric contents.

3.1.12. Parenteral anti-ulcerant (Injection) in patient with severe hyperacidic conditions or patients who are unable to take oral therapy

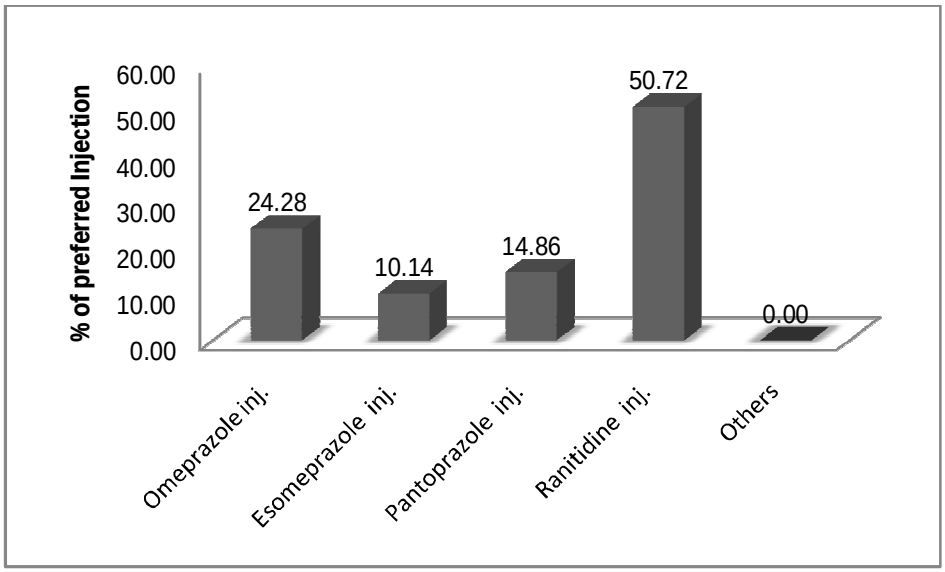


Fig.-3.2 preferred parenteral anti-ulcerant in severe hyperacidic conditions

According to statistical analysis, we can found that 50.72 % of prescribers preferred Ranitidine injection in patient with severe hyperacidic conditions or patients who are unable to take oral therapy. Then Omeprazole is in second position, Esomeprazole is in third position and Pantoprazole injection is in forth position.

Chapter Four:

DISCUSSION & CONCLUSION

Result & Discussion

From the total collected data, we can estimate the % of preferred molecules for gastrointestinal acid related disorders. The estimate is given below. It is found that from the survey statistical analysis, the first preferred molecules is Omeprazole, second Ranitidine, third Pantoprazole etc. as below-

Omeprazole > Ranitidine > Esomeprazole > Pantoprazole > Rabeprazole > Lansoprazole > Famotidine

Table 4.1: % of preferred molecules by physicians estimated from survey

Molecule	Frequency	%	Total
Omeprazole	959	42.17	
Ranitidine	550	24.19	
Esomeprazole	512	22.52	
Pantoprazole	148	6.51	2274
Rabprazole	59	2.59	
Lansoprazole	40	1.76	
Famotidine	6	0.26	

Similarly from the IMS data 3Q, 2011 we can estimate the Share (%) of different molecules from the total market of anti-ulcerants. We can found that according to market share, Omeprazole is in the first position; Esomenta is in second position, etc. The positions are given below in order-

Omeprazole > Ranitidine > Esomeprazole > Pantoprazole > Rabeprazole > Lansoprazole > Famotidine.

Table 4.2 : Share (%) of molecules estimated from total antiulcerant market

Name	Value	Share (%)	Total value
Omeprazole	5,089,228,932	42.34	
Ranitidine	2,450,049,037	20.38	
Esomeprazole	2,260,894,212	18.81	
Pantoprazole	1,412,973,928	11.76	12,019,526,249
Rabprazole	568,386,055	4.73	
Lansoprazole	170,619,336	1.42	
Famotidine	67,374,749	0.56	

Now from the two sample data, we can compare the survey result and IMS data.

From the survey data we get the estimate of preferred antiulcerant molecules for different gastrointestinal acid related disorders. We get an idea of prescription pattern of different molecules.

From the IMS data we can get the estimation of the market and share of different anti-ulcerant molecules.

From the two tables first data is-DIFFERENT TYPES OF MOLECULES PRESCRIBED BY PHYSICIANS IN GASTROINTESTINAL ACID RELATED DISORDER

& the second data is-DIFERENT TYPES OF MOLECULES ACTUALLY CONSUMED BY PATIENTS

From the molecules order of both tables above, it is very clear that our data from survey is similar to IMS data. Because both order is as-

Omeprazole > Ranitidine > Esomeprazole > Pantoprazole > Rabeprazole > Lansoprazole > Famotidine.

Then % (share) in both data is almost same for all the given molecules.

After statistical analysis (T-Test of the above data),

P value is-0.5

So null hypothesis is accepted as the probability of error is quite high (greater than 0.05). That means there is no difference in the both samples means. It is determined that two samples are likely to have come from the same two underlying populations that have the same mean.

Similarly we get the same findings from the Injection share (Survey data and IMS data)

Table 4.3: % of preferred Injection estimated from survey

Injection	Frequency	%	Total
Omeprazole inj.	296	53.62	552
Ranitidine inj.	154	27.90	
Esomeprazole inj.	63	11.41	
Pantoprazole inj.	39	7.07	

Table 4.4 : Share (%) of injection molecules estimated from total antiulcerant market

Injection	Frequency	%	Total
Omeprazole inj.	5,982,856,132	44.98	13,300,306,729
Ranitidine inj.	3,152,925,585	23.71	
Esomeprazole inj.	2,886,456,618	21.70	
Pantoprazole inj.	1,278,068,394	9.61	

After statistically analysis (T-Test of the above data),

P value is also-0.57

So accept the null hypothesis as the probability of error is quite high (greater than 0.05). That means there is no difference in the both samples means. it is determined that two samples are likely to have come from the same two underlying populations that have the same mean.

Conclusion:

Finally we can understand that proton pump inhibitors are the first choice for prescribers for acid related disorder. Different types of proton pump inhibitors like- Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole and Rabeprazole are prescribed in different patients group and acid related diseases. From PPIs most of the prescribers preferred Omeprazole for its trusted efficacy & safety profile. But day by day Esomeprazole prescription is increasing in locally and obroad. Its market is growing day by day for its superior intra-gastric pH control, least side effects. Still now Ranitidine market is large but there is lowest prescription accept injection. It is consumed by patients as OTC drug. In present Antacids prescription rate is very rare. It is used only as OTC drugs in Bangladesh.

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