PHARMACOTHERAPY OF PEPTIC ULCER AND PRESCRIPTION OF ANTI ULCER DRUGS IN VARIOUS DISEASES

A

PROJECT REPORT

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“you want to do the right thing &
you want to do it for right reason
but if you don’t have right guidance
you can never hit the right target.”

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Only with your friends.”

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1. INTRODUCTION

Peptic ulcer disease (PUD) is a common disorder that affects millions of individuals in the United States each year, with a major impact on health care costs. In the last two decades, major advances have been made in the understanding of the pathophysiology of PUD, particularly regarding the role of *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drugs (NSAIDs). This has led to important changes in diagnostic and treatment strategies, with the potential for improving the clinical outcome and decreasing health care costs.

A peptic ulcer is a mucosal break, 3 mm or greater in size with depth, that can involve the stomach or duodenum. The most important contributing factors are *H pylori*, NSAIDs, acid, and pepsin. Additional aggressive factors include smoking, ethanol, bile acids, aspirin, steroids, and stress. Important protective or defensive factors are mucus, bicarbonate, mucosal blood flow, prostaglandins, alkaline tide, hydrophobic layer, restitution, and epithelial renewal. When an imbalance occurs, PUD might develop.

**Frequency:**

**In the US:** One-year point prevalence is 1.8%. Lifetime prevalence is approximately 10%. PUD affects approximately 4.5 million people annually.
Internationally: The frequency of PUD in other countries is variable and determined primarily by association with the major causes of PUD: *H pylori* and NSAIDs.

**Mortality/Morbidity:** Physician office visits and hospitalizations for PUD have decreased in the last few decades. The mortality rate has decreased modestly in the last few decades and is approximately 1 death per 100,000 cases. The hospitalization rate is approximately 30 patients per 100,000 cases.

**Sex:**

Prevalence has shifted from predominance in males to similar occurrences for both sexes. Lifetime prevalence is approximately 11-14% for men. Lifetime prevalence is approximately 8-11% for women.

**Age:**

Age trends for ulcer occurrence reveal declining rates in younger men, particularly for duodenal ulcer, and increasing rates in older women. Trends reflect complex changes in risk factors for PUD, including age-cohort phenomena with the prevalence of *H pylori* infection and the use of NSAIDs in older populations.

**Physical:**

In uncomplicated PUD, clinical findings are few and nonspecific. Epigastric tenderness, Guaiac-positive stool resulting from occult blood loss, There is melena resulting from acute or
subacute gastrointestinal bleeding, Succussion splash resulting from partial or complete gastric outlet obstruction.

**Causes:**

1. *H pylori* infection

   It is Most common cause of PUD, Associated with as many as 90% of duodenal ulcers and 70-75% of gastric ulcers

2. **Nonsteroidal anti-inflammatory drugs**

   They are Second most common cause of PUD, Addition of steroids with NSAIDs potentiates risk, It Accounts for the majority of *H pylori*–negative ulcers

3. Severe physiologic stress, Burns, CNS trauma, Surgery, and severe medical illness

4. Hypersecretory states (uncommon)

5. It includes Gastrinoma (Zollinger-Ellison syndrome) or multiple endocrine neoplasia (MEN-I), Antral G cell hyperplasia

6. Systemic mastocytosis

7. Basophilic leukemias

8. Diseases associated with an increased risk of PUD include cirrhosis, chronic pulmonary disease, renal failure, and renal transplantation.
9. Additional rare, miscellaneous causes include radiation-induced or chemotherapy-induced ulcers, vascular insufficiency (crack cocaine), and duodenal obstruction.

**Major Complications:**

- Perforation
- Penetration
- Obstruction
- Bleeding

**Prognosis:**

When the underlying cause is addressed, the prognosis is excellent. Most patients are treated successfully with the cure of *H pylori* infection, avoidance of NSAIDs, and the appropriate use of antisecretory therapy. Cure of *H pylori* infection changes the natural history of the disease, with a decrease in the ulcer recurrence rate from 60-90% to less than 10% per year (in some reports, recurrence is 1-2%).

### 2. PHYSIOLOGY AND PATHOGENESIS

#### 2.1 Peptic ulcer:-

The "**acid pepsin mixture**" means the *stomach* secretes both hydrochloric acid (HCL) and pepsin (the proteolytic enzyme). HCL is secreted by the parietal cell whereas pepsin (as pepsinogen) by the
peptic cell. Both the parietal and peptic cell is normally present in the gastric mucosa. The pepsin can digest protein only when the PH is sufficiently low, between PH 2-3. At higher PH (>5), pepsin becomes inactive and cannot digest protein. Therefore, presence of a strong acid like HCL is necessary.

In the gastric mucosa, as well as in the 1st part of the duodenum, there is “defence mechanism: In normal persons the defence mechanism is adequate so no ulcer develops.

![Gastric mucosal barrier](image)

**Fig.1 Gastric mucosal barrier**

It follows (Fig 1.) where the defence mechanism is weakened; or the aggressive mechanism, ie. The Acid Pepsin Mixture (APM), is strengthened, peptic ulcer should develop.

Note, in the lower esophagus, no ulcer normally develops, because the Lower Esophageal Sphincter (LES) is ordinarily active enough so that reflux (from stomach to esophagus) does not occur. Also in the 2nd part of duodenum, because of arrival of pancreatic and biliary
secretion, the HCL of the gastric chyme is neutralized, the pH raised and pepsin becomes inactive.

2.1.1 Components of the Gastric defence mechanism.

There are,

(i) The gastric mucus
(ii) The HCO₃⁻ secretion by the gastric mucosal cells
(iii) The vasculature and
(iv) Presence of ‘tight junctions’ between the epithelial cells of the stomach and duodenum.

Gastric mucus (Fig:1) Forms a layer over the epithelium of the mucosa. Some mucosal cells of the pyloric region of the stomach secretes bicarbonate ions which remain in between the epithelial cells and the mucus (Fig:1) and pH at this spot is considerably high, may be 6 or 7. Therefore, in the luminal surface of the mucus, the pH is low, say about 2 or 3, the peptic activity is high, digestion is possible. On the other hand, near the epithelium, i.e., deep to the mucus layer, the pH is high, pepsin loses its activity. It follows, any condition which depolymerizes the mucopolysaccharide molecules of the mucus, (thus causing reduction of stickiness of the mucus) lowers the defence barrier. One such agent is NSAIDs (depolymerizes the mucus).

Mechanical barrier offered by the mucus present on the surface of gastric epithelium is very important component of the defence. If this mucus is thick and sticky, the APM fails to penetrate it APM does not reach close to the epithelial cells (Fig.1) no digestion of the epithelial
cells. Recall, pepsin molecules are big, they require good deal of space through which they can traverse (though the mucus). Normally mucopolysaccharide molecules are polymerized in the gastric mucus. Depolymerization causes loss of their stickiness and increases permeability to pepsin. NSAIDs and aspirin by inhibiting the synthesis of PGE$_2$ and PGI$_2$ cause depolymerization of the mucopolysaccharide polymers.

The junction between the epithelial cells of the gastric mucosa is tight (conversely, in the small intestine, it is leaky) as known in (Fig.1). Nothing passes through them. Recall, because of the high acidity, aspirin is better absorbed in the stomach. While it being absorbed, aspirin(i) damages the tight junction in between the cells (Fig.1) and (ii) inhibits the synthesis of prostaglandins within the gastric epithelial cell. This two effects weaken the gastric defence mechanism.

2.1.2 AGGRESSIVE FACTORS:-

2.1.2.1. H.PYLORI:
In recent times Helicobacter pylori has captured attention. H.Pylori is a gm-ve bacteria found in the gastric and duodenal mucosa of most persons, particularly the elderly. They, while in the mucosa, spilt urea into ammonia and thus elevates the local pH. Damage of the local region of the mucosa by high alkalinity. In this way, they strongly help the peptic ulcer studied, H.Pylori has been recoverd from the duodenal mucosa. Consequently, antibiotics (eg. Metronidazole) which kill H.Pylori, are popular against peptic ulcer.

2.1.2.2. ACID:
HCL is secreted by the parietal cells of the gastric glands. To be remembered is that if the activity of pepsin is inhibited the digestive ability of APM is remarkably reduced. Consequently, drugs (H$_2$ blocker, proton pump inhibitors, antacids and so on ), which, ultimately either inhibit HCl secretion or neutralize the secreted HCl, are very popular in the pharmacotherapy of peptic ulcer.

Therefore, some details of HCl secretion needs recapitulation:

- H$^+$ ion is generated from HOH (i.e., water) within the parietal cells. Cl-ion is obtained from NaCl of the adjacent capillary blood. The two ions unite within the canaliculus of parietal cell to form HCl and now the HCl flows into the lumen (Fig:2). Note, in Fig;2, the H$^+$ ion generated from H$_2$O molecule within the parietal cells is pumped into the canaliculus by a Proton pump (proton=H$^+$). Proton pump is Na$^+$K$^+$ATPase, i.e., because of the action of Na$^+$K$^+$ATPase enzyme, the H$^+$ is pumped from the cell to the canaliculus.

- Stimulants/inhibitors of gastric HCl. (i) Parietal cells are supplied by vagal fibers. Stimulation of vagus causes HCl secretion from the parietal cells. The neurotransmitter at the vagal terminal is acetyl choline (Ach) and the receptors at parietal cell are muscarinic. (ii) Parietal cells also contain gastric receptors on their surface. Combination of gastric with these receptors causes parietal cell stimulation → production of HCl. Gastric (a GI hormone) is produced by G cells, found in the antral region of gastric mucosa and mucosa of the 1$^{st}$ part of duodenum. (iii) Histamine stimulates the HCl
secretion. Histamine (H) is produced by mast cell situated very close to parietal cells. Parietal cells contain histamine receptors.

- Parietal cells also contain (i) Somatostain and (ii) prostaglandin receptors. Both somatostatin and prostaglandin are inhibitors of HCl secretion. Somatostatin is secreted by D cells of the gastric antral mucosa.

D and G cells lie side by side and exert a paracrine effect on each other.

Other notable factors influencing HCl secretion include (1) calcium, (2) alcohol, (3) coffee, (4) acidity of the gastric content and (5) food fat. Calcium, given orally, can cause gastric stimulation. Milk diet, which was once a sheet anchor of peptic ulcer therapy, is, therefore, no longer favored for peptic ulcer. Role of gastric acidity and food fat has been given below.

Importance of gastric acidity, food fast and GI hormones are particularly noteworthy.

(1) Any condition, which makes the content of the stomach strongly acidic, reduces gastric secretion→ inhibition of gastric HCl; it is thus a Nature’s safety mechanism. Conversely, if the pH of the gastric content is higher, gastric is liberated more and more. When the pH < 3.0 gastric secretion is remarkably low, if pH < 1.5, gastric secretion is abolished. This is important; use an agent (eg. an alkali)
to neutralize the HCl $\rightarrow$ gastric pH is raised $\rightarrow$ but now rebound acidity develops $\rightarrow$ purpose of alkali administration is largely defeated:

(2) The Ayurvedic people used “Dugdhra patpati” (in which the peptic ulcer patient had to drink, say, 5 liters of milk per day) treatment, which was also, in its less vigorous intensity, used by our forefathers too, till recently. Heavy fat (as in large quantity of milk ingestion) causes inhibition of gastric HCl secretion. Fat produces release of some yet undetermined GI hormones (enterogastone), may be GIP, which inhibits gastric HCl secretion. Milk therapy, now, however, is unpopular.

Some further details about histamine (H), may be noted: Histamine receptors are of two types:

(i) H1 (present in vascular smooth muscles/bronchial muscles/brain neurons) and

(ii) H2 receptors (present on parietal cells/uterine muscles/brain neurons).

Stimulation of H1 receptors causes (i) Vasodilation (ii) Bronchospasm; recall the signs of anaphylactic shock. Stimulation of H2 receptors causes HCl secretion from parietal cell because H2 Receptors inhibit gastric secretion.

Histamine is secreted, as stated above, by mast (also called, enterochromaffin like-ECL) cells situated very close to the parietal cells. Gastric can stimulate the ECL cells to produce Histamine and the Histamine in turn stimulates the parietal cell to produce HCl. Ach also behaves like gastric. The situation can be summarized by a flow chart (Fig:2)
Viewed in this way, histamine is sometimes called the, “final common path”, because both gastric and Ach act, largely via the Histamine. However, all authorities do not agree that Histamine is the final common path. Nevertheless, if H$_2$ blockers are used (Fig:2) effects of gastric and Ach on HCl secretion are very much (but probably not totally) blunted. For all these reasons, H$_2$ blockers have assumed a supreme role in peptic ulcer pharmacotherapy.

Role of prostaglandins(PGs). In the past, importance of PGs was not fully appreciated. Gastric mucosal cells secrete heavy amounts of PGs. The major known effects of PGs, particularly of the E series, include:

(i) Increased gastric mucus secretion,
(ii) Increased gastric HCO$_3^-$ secretion,
(iii) Better blood flow in the gastric mucosa and
(iv) Helping to grow the new normal epithelial cells. Recall, normally,

The epithelial cells of the stomach have a life span of only about 5 days, so that they continuously die and are cast off and new epithelial cells grow to replace the cast off cells. Common sense logic suggest that smooth development of new cells (to replace the dead cells) will help in speedier and better healing of an erosion.

2.1.2.3. PEP SIN:

Pepsin is secreted by peptic and even mucus cells of the gastric glands. Therefore, parietal cell produced HCl and intrinsic factor but no pepsin whereas peptic cell produce pepsin but no HCl. Pepsin (at least 2 groups of pepsinogens are known) is produced from pepsinogen, provided the environment (medium) is strongly acid.
Also, Pepsin activity (peptic activity) can occur only in strongly acidic medium. Pepsin is the ultimate digesting (proteolytic) enzyme. Hence, elevation of the gastric pH blunts peptic activity.

Most factors, which stimulate gastric HCl secretion, also stimulate peptic secretion. In particular vagal stimulation, i.e., cholinergic stimulation, is one such.

2.1.3 BALANCE BETWEEN PROTECTIVE & EROSGE FACTOR:-

Recently, much more attention has been focused on the factors responsible for the maintenance of mucosal integrity. These include
the secretion of bicarbonate-laden mucus and the turnover of mucosal cells every 36-48h, both factors depending on an adequate blood supply. These bile reflux, chronic gastritis (from gastric stasis, diet or alcohol), local ischaemia and hyperacidity (40%). This balance is illustrated in Fig:2.1.3.. The damage caused to the mucosal by reflux of bile through an incompetent pyloric sphincter possibly accounts for the high incidence of ulcers in the pyloric antrum.

The role of Helicobacter Pylori has already been mentioned. These are also been considerable recent interest in the role of prostaglandins. Some of these have been shown, in animal studies to inhibits acid secretion in small doses. Promote the repair of damaged gastric mucosa and to stimulate gastric blood flow. They have therefore been described as “Cytoprotective agents” through there is considerable debate as to whether this description is justified. This explains why NSAIDs which inhibit prostaglandin synthesis, are ulcerogenic.

2.2 Duodenal ulcer:-
Duodenal ulcer is an ulcer in the wall of the duodenam, rarely malignant, extending into the muscularis mucous. Practically all the duodenal ulcer is occur in the duodenal bulb. Ulcer that are occur beyond the bulb are uncommon and are called postulbar ulcer. About 20% of patients have multiple Du`s. Duodenal ulcer usually are round or oval and less than 1 cm in diameter, but may be larger and irregular in shape.
The true cause of Du is unknown, although it has been assumed for years that they are related to excessive parietal cell HCl secretion. This could result from increased parietal cell mass increased gastric emptying rate or defective inhibition of acid secretion. Only one third to one half of patients with Dus have excessive acid secretory rates as evidenced by basal gastric hypersecretion and increased peak acid secretion.

Du is both chronic and recurrent approx 60% of healed to 90% within 2 years. Dus probably represent a stage in a dynamic disease process that begins with acute inflammation of the duodenal mucosa and progresses through more severe stages of duodenitis until an ulcer develops. The ulcer usually persists for 4 to 6 weeks but may an occasion heal rapidly. The whole process may repeat itself. Certain risk factors such as cigarette smoking, chronic use of aspirin and other NSAIDs or alcohol contribute to increased risk of ulcer development. Genetic factor appears to be important, with first degree relatives of patients with Dus developing ulcer three times as often as the general population. Smokers have a higher and more frequent mortality. A variety of stress situations appear to be weakly associated with new ulcer development.
2.3 Drugs Affecting Gastric Acid Secretion
Pharmacotherapy of Peptic Ulcer and Prescription of Anti-Ulcer Drugs in various Diseases

Fig: 2 Drugs Affecting Gastric Acid Secretion

1. mucosal coating agents (sucralfate)
2. antacids
3. H2-receptor blockers
4. proton-pump inhibitors
5. prostaglandin analogs (misoprostol)
6. muscarinic receptor antagonists (anticholinergics)
3. Signs And Symptoms

The symptoms of a peptic ulcer vary and, by themselves, are not a reliable way to tell whether you have an ulcer. Also, some people may not have symptoms.

The symptoms of an ulcer, such as dyspepsia, often can be confused with other abdominal conditions, such as dyspepsia or gastroesophageal reflux disease (GERD).

Common ulcer symptoms include:

- A burning, aching, gnawing pain between the navel and the breastbone. The pain sometimes extends to the back.
- Abdominal pain that can last from a few minutes to a few hours and usually goes away for a while after taking an antacid or acid reducer.
- Weeks of pain that comes and goes and may alternate with pain-free periods.
- Loss of appetite and weight loss.
- Bloating or nausea after eating.
- Vomiting after meals.
- Black, tarlike stools or stools containing dark red blood if the ulcer is bleeding.

Symptoms of ulcers in the upper small intestine (duodenal ulcers) and in the stomach (gastric ulcers) are similar, except for when pain occurs.
Pain from a duodenal ulcer may occur several hours after eating (when the stomach is empty) and may improve after eating. Pain also may wake you frequently in the middle of the night.

Pain from a gastric ulcer may occur shortly after eating (when food is still in the stomach).

Some ulcers do not cause symptoms. These are known as silent ulcers.

As many as half of all peptic ulcers do not cause any symptoms until a complication develops. Complications of an ulcer may include bleeding, perforation, penetration, or obstruction of the digestive tract.

Silent ulcers are more common in older adults, people who have diabetes, or people who use large amounts of nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin.

In children, symptoms vary with age:

- Toddlers and young children may complain of general stomach pain.
- Teenagers may have symptoms more like those experienced by adults.

4. Diagnosis
The tests needed to diagnose peptic ulcer disease may depend on symptoms and on a medical history and physical exam.

In a younger adult who is having ulcer symptoms for the first time, health professional may begin treatment with medications based only on symptoms and the results of medical history and physical examination. However, it is becoming more common to test immediately for Helicobacter pylori (H. pylori) infection whenever someone has ulcerlike symptoms.

In older than age 45, may require more extensive testing because the patient may be at increased risk for stomach cancer. Although the risk of stomach cancer is small, it is important to distinguish between a gastric and duodenal ulcer because a gastric ulcer that does not respond to treatment could be cancer. Early diagnosis of stomach cancer is essential for successful treatment. Additional testing is needed especially for those people over 45 who have:

- Ulcer symptoms for the first time.
- Ulcer symptoms that return before or after treatment is completed.
- Family history of stomach cancer.
- Additional symptoms that may indicate a more serious problem such as stomach cancer. These include
  - Blood in the stool.
  - Weight loss of more than 10% of body weight.
  - Anemia.
4.1 Tests to diagnose peptic ulcer disease

When a person has symptoms of a peptic ulcer, the following tests are used:

- **Upper gastrointestinal (UGI) series.** An X-ray exam of the esophagus and stomach (**upper GI series**) may be used to diagnose peptic ulcer disease, although this test is being used less frequently.

- **Endoscopy.** Endoscopy allows the doctor to look at the inside of the stomach and upper small intestine to see whether ulcers are present. It also allows the doctor to collect a tissue sample (biopsy) that can be tested for the presence of *H. pylori* bacteria or other problems (such as cancer) in the stomach.

A **fecal occult blood test (FOBT)** may be done to detect blood in the stool, which may be caused by a peptic ulcer or another serious problem, such as colon cancer. By itself an FOBT cannot diagnose peptic ulcer disease, but it may indicate if an ulcer is bleeding.

A **complete blood count (CBC)** also may be done to look for anemia, which may be caused by a bleeding ulcer.
4.2 Tests for H. pylori infection

Many people are infected with *H. pylori* bacteria, but most of them will not develop symptoms of peptic ulcer disease. Because of this, testing for *H. pylori* infection is recommended only in people who: Have active peptic ulcer disease or a past history of a peptic ulcer.

- Are known to have or have a family history of stomach cancer or another condition called mucosa-associated lymphoid tissue (MALT).
- Have a new case of *dyspepsia*. *H. pylori* testing may not be of value for *dyspepsia* not caused by an ulcer.
- Are willing to begin treatment if bacteria are found.

However, some doctors prefer to test for *H. pylori* infection in everyone who has ulcer-like symptoms.

Doctor may recommend a screening for *H. pylori* before long-term NSAID use is begun. Screening and treatment for *H. pylori* infection has been shown to reduce the risk of ulcers for people starting long-term NSAID use. Anyone taking NSAIDs should discuss the potential risks of long-term NSAID use with their health professional.

*Helicobacter pylori* tests cannot diagnose peptic ulcer disease or other conditions that may cause symptoms similar to an ulcer. These tests can only determine whether *H. pylori* bacteria
are present. The most common tests used to detect an infection with \textit{H. pylori} bacteria include:

- **Biopsy of the stomach lining.** During an upper endoscopy exam, a biopsy of the stomach lining will be collected to test for \textit{H. pylori} bacteria. A biopsy is the most accurate way to test for \textit{H. pylori}. It also allows the doctor to check for other possible causes of symptoms (such as cancer). A biopsy is expensive and requires an upper endoscopy exam, which is more invasive than other tests used to detect \textit{H. pylori}.

- **Blood test for \textit{H. pylori} antibodies.** A blood test for \textit{H. pylori} antibodies is a quick, easy, and inexpensive test to detect them. This blood test may make it possible to avoid having an upper endoscopy exam. However, it cannot distinguish between a past or current infection with \textit{H. pylori} bacteria; therefore, it is not useful for determining whether an infection has been cured.

- **Urea breath test.** A urea breath test for \textit{H. pylori} is very accurate. Unlike the blood test, it will detect only those \textit{H. pylori} bacteria that are present at the time of the test. This makes it a good test for checking to see whether an \textit{H. pylori} infection has been cured. The test is somewhat expensive.

- **Stool antigen test.** This test checks for antigens for \textit{H. pylori} in the stool. It can be used to diagnose \textit{H. pylori} bacteria as a cause of peptic ulcer disease and to see whether treatment has eliminated the infection.
5. TREATMENT

Some people who have received therapy with medications to treat an *H. pylori* infection may need follow-up testing to ensure the infection.

If the patient have been diagnosed with a peptic ulcer due to infection with *Helicobacter pylori* (*H. pylori*) bacteria, the patient will need treatment with antibiotic medications to kill or control the bacteria.

- If ulcer is due to use of nonsteroidal anti-inflammatory drugs (NSAIDs), stop using them if possible. NSAIDs can slow or prevent the healing of an ulcer.
- Medications that reduce the amount of acid produced by the stomach are used to treat all forms of peptic ulcer disease.
These include histamine H$_2$ acid reducers and proton pump inhibitors.

- Lifestyle changes, such as quitting smoking, limiting caffeine and alcohol intake, and reducing stress, can help speed the healing of your ulcer and prevent it from recurring.
- Ulcers that do not respond to treatment may have developed complications, or may actually be cancer. The patient may need an endoscopy so that doctor can look at the inside of stomach and upper small intestine to check for *H. pylori*, or to collect a tissue sample (biopsy) that can be tested for cancer.
- If an ulcer eats through the wall of the stomach or intestine into the abdominal cavity (perforation), or if ulcer continues to bleed despite therapy, patient may require surgery. However, these complications are rare.

Many cases of peptic ulcer disease are caused by an infection with *Helicobacter pylori* (*H. pylori*) bacteria or use of nonsteroidal anti-inflammatory drugs (NSAIDs). Medications that reduce the amount of acid produced by the stomach are used to treat all forms of peptic ulcer disease. If an *H. pylori* infection is present, antibiotics to eliminate the infection are used in combination with these medications.

Taking nonprescription medications and making some lifestyle changes also can help speed the healing of an ulcer and reduce the risk that it will come back.
5.1 Initial Treatment

Initial treatment of peptic ulcer disease depends on its cause.

- **H. Pylori infection.** Treatment to eliminate Helicobacter pylori (H. pylori) bacteria usually involves combining two antibiotics with an acid reducer such as a proton pump inhibitor or sometimes a bismuth compound. Curing the infection speeds the healing of an ulcer and makes the ulcer less likely to recur. It is important to receive the proper combination of antibiotics to cure the infection; if the bacteria are not eliminated by the antibiotics, they may become even more difficult to kill later (resistant).

- **NSAIDs.** If at all possible, you will need to stop taking large amounts of nonsteroidal anti-inflammatory drugs (NSAIDs). In some cases NSAIDs with a lower risk for causing ulcers may be substituted. These include COX-2 inhibitors (such as rofecoxib and celecoxib) that reduce inflammation and pain without causing as much gastrointestinal damage as other NSAIDs. If you must continue taking an NSAID, other
medications may be used to protect the stomach. See the Medications section of this topic for more information.

- **Hypersecretory condition.** Acid reducers are most often used to treat an ulcer caused by a hypersecretory condition (a condition in which stomach produces excessive acid). In addition, doctor may want to conduct other tests to determine whether there is another cause for the ulcer.

- **Unknown cause.** If no cause can be found (idiopathic ulcer), ulcer will usually be treated with an acid reducer. Long-term treatment depends on the severity of the ulcer and other factors, such as the size of the ulcer, whether patient have had complications, and what other treatments have been used.

Whatever the cause of ulcer, patient need to stop taking large amounts of NSAIDs if possible. NSAIDs have been shown to cause peptic ulcers. Certain lifestyle changes, such as quitting smoking, limiting caffeine and alcohol intake, and reducing stress, can help speed the healing of an ulcer and make sure it doesn't come back.

Most treatments will be continued for 4 to 8 weeks, depending on various factors including the size of the ulcer.

**Ongoing treatment**

If patient continue to use nonsteroidal anti-inflammatory drugs (NSAIDs) after being diagnosed with a peptic ulcer, work with
doctor to find an alternative pain reliever. Use of NSAIDs can slow the healing of an ulcer or prevent it from healing altogether. If patient must continue to use NSAIDs, doctor may recommend to take a prostaglandin analog, such as misoprostol, or a proton pump inhibitor. Misoprostol reduces the amount of acid produced by the stomach and protects the stomach lining without reducing the effectiveness of NSAIDs in treating other conditions such as arthritis.

If ulcer symptoms do not respond to treatment, follow up with doctor to be sure Helicobacter pylori (H. pylori) bacteria have been identified and treated. Most peptic ulcers are caused by infection with H. pylori bacteria. Persistent infection will likely be treated with an alternate combination of medications. Antibiotic treatment for H. pylori should be taken exactly according to doctor's instructions for it to be effective.

Tests such as the urea breath test and a stool antigen test can determine whether an H. pylori infection has been cured. If patient have a history of ulcer complications or a family history of stomach cancer, he may need an endoscopy so that doctor can look at the inside of stomach and upper small intestine to see whether an ulcer is present. An endoscopy can also be used to collect a tissue sample (biopsy) that can be tested for H. pylori or cancer. See the Exams and Tests section of this topic for more information on these tests.
In addition, certain lifestyle changes, such as quitting smoking, limiting caffeine and alcohol intake, and reducing stress, can help speed the healing of an ulcer and make sure it doesn't come back.

5.1.1 General Medical Care:

- Given current understanding of the pathogenesis of PUD, the majority of patients with PUD are treated successfully medically with cure of \( H\ pylori \) infection and/or avoidance of NSAIDs, along with appropriate use of antisecretory therapy.

- A number of treatment options exist for patients presenting with symptoms suggestive of PUD or ulcerlike dyspepsia, including empiric antisecretory therapy, empiric triple therapy for \( H\ pylori \) infection, endoscopy followed by appropriate therapy based on findings, and \( H\ pylori \) serology followed by triple therapy for infected patients.

- Computer models have suggested that obtaining an \( H\ pylori \) serology followed by triple therapy for those infected is the most cost-effective approach; however, no direct evidence from clinical trials confirms this.

- Perform endoscopy early in patients older than 45-50 years and in patients with associated so-called alarm symptoms, such as dysphagia, recurrent vomiting, weight loss, or with signs of bleeding.
5.1.2 General Surgical Care: With the success of medical therapy, surgery has a very limited role in the management of PUD.

- Potential indications for surgery include refractory disease, and complications of PUD include the following:
  - Refractory, symptomatic peptic ulcers, though rare with the cure of *H. pylori* and the appropriate use of antisecretory therapy, are a potential complication of PUD.
  - Perforation usually is managed emergently with surgical repair. However, this is not mandatory in all patients.
  - Obstruction can complicate PUD, particularly if PUD is refractory to aggressive antisecretory therapy, *H. pylori* eradication, or avoidance of NSAIDs. Obstruction may persist or recur despite endoscopic balloon dilation.
  - Penetration, particularly if not walled-off or if a gastrocolic fistula develops, is a potential complication of PUD.
  - Bleeding can complicate PUD, particularly in patients with massive hemorrhage and hemodynamic instability, recurrent bleeding on medical therapy, and failure of therapeutic endoscopy to control bleeding.

- The appropriate surgical procedure depends on the location and nature of the ulcer.
Many gastroenterologists recommend simple oversewing of the ulcer with treatment of underlying *H pylori* infection or cessation of NSAIDs for bleeding PUD.

Additional surgical options for refractory or complicated PUD include vagotomy and pyloroplasty, vagotomy and antrectomy with gastroduodenal reconstruction (Billroth I) or gastrojejunal reconstruction (Billroth II), or a highly selective vagotomy.

### 5.1.3 Treatment if the condition gets worse

Recurring ulcers will likely be treated with an alternate combination of medications. Doctor may conduct follow-up tests to determine whether an infection with *Helicobacter pylori* (*H. pylori*) has continued or returned. Tests for *H. pylori* include testing your breath, stool, and blood, and a biopsy of your stomach lining. See the Exams and Tests section of this topic for more information on these tests.

If patient have experienced significant complications from a peptic ulcer such as bleeding or obstruction, may need an endoscopy, even if patient have already had one. If stomach or intestine has a perforation, or ulcer continues to bleed despite treatment, patient may require surgery. However, surgery is rarely used to treat an ulcer.

### 5.2 DRUGS USED IN PEPTIC ULCER
### Mucosal Coating Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sucralfate</td>
<td>- Sucrose polymer</td>
</tr>
<tr>
<td></td>
<td>- Binds to glycoproteins on ulcer, pepsin, bile acids</td>
</tr>
<tr>
<td></td>
<td>- Impedes diffusion of acid</td>
</tr>
<tr>
<td></td>
<td>- Only 5% absorbed into circulation</td>
</tr>
<tr>
<td></td>
<td>- S/E: constipation, aluminum toxicity in renal disease, reduces absorption of other drugs (i.e. tetracyclines)</td>
</tr>
</tbody>
</table>

### Antacids

<table>
<thead>
<tr>
<th>Type</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltsofcarbonate</td>
<td>- Neutralize stomach acid</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>- Al(OH)3 can cause constipation</td>
</tr>
<tr>
<td>Citrate</td>
<td>- Mg(OH)2 can cause diarrhea</td>
</tr>
<tr>
<td>Phosphate</td>
<td>- Ca salt derivatives can cause Ca ppt. In urine, reduce PTH, increase gastric rebound</td>
</tr>
<tr>
<td>Trisilicate</td>
<td>- Na salts not good for someone on low salt diet</td>
</tr>
</tbody>
</table>

### H2 Receptor Blockers

<table>
<thead>
<tr>
<th>Effect</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reduce: volume, [H⁺], pepsin</td>
</tr>
</tbody>
</table>
Pharmacotherapy of Peptic Ulcer and Prescription of Anti-Ulcer Drugs in various Diseases

- Ranitidine
- Famotidine
- Nizantidine
- Cimetidine

- Effective on: fasting, nocturnal, stimulated (meals) acid
- All have similar efficacy, but different potency, duration, side effects, costs
- 4 - 8 wk therapy
- S/E (rare): headache, dizziness, nausea, skin rash, itching
- Cimetidine binds 450 and inhibits metabolism of: warfarin, phenytoin, theophylline, phenobarbital, many benzodiazepines, propranolol, nifedipine, digitoxin, quinidine, TCAs), has an anti-androgen effect

<table>
<thead>
<tr>
<th>Proton Pump Inhibitors (PPI)</th>
<th>Reduces $[X^+]$, not volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Most potent agent for reducing</td>
</tr>
</tbody>
</table>
Pharmacotherapy of Peptic Ulcer and Prescription of AntiUlcer Drugs in various Diseases

<table>
<thead>
<tr>
<th></th>
<th>stomach acid</th>
<th>ph sensitive granules release drug at pH &gt; 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>Prodrug activated by acid and binds to -SH groups irreversibly on proton pump</td>
<td>Inhibits cyt P450 and prolongs metabolism of certain drugs (i.e. diazepam, phenytoin)</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Can lead to modest hypergastrinemia</td>
<td>Can use in Zollinger-Ellison syndrome</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>3% get nausea, diarrhea, headache, bacterial overgrowth</td>
<td></td>
</tr>
</tbody>
</table>

Prostaglandin Analogs

<table>
<thead>
<tr>
<th></th>
<th>Mainly used to prevent complications of NSAID therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misoprostol</td>
<td>Increases mucus, bicarbonate</td>
</tr>
<tr>
<td></td>
<td>Reduces acid, cAMP</td>
</tr>
<tr>
<td></td>
<td>S/E: can stimulate uterine activity, contraindicated in women of childbearing potential</td>
</tr>
</tbody>
</table>

S.K. Patel Colledge Of Pharmaceutical Education and Research, Kherva.
5.3 Medications

Most peptic ulcers can be cured and prevented from returning by eliminating Helicobacter pylori (H. pylori) infections and by avoiding use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Medications are used to:

- Treat peptic ulcer disease by reducing the amount of acid produced by the stomach.
- Kill H. pylori bacteria when it is determined they are infecting the stomach lining.
- Prevent NSAID-related peptic ulcer disease by helping protect the lining of the stomach and upper small intestine (duodenum) from injury caused by NSAIDs.

Medication Choices

Medications to reduce acid production

Medications that reduce the amount of acid produced by the stomach are used to treat all forms of peptic ulcer disease.

- Histamine H2 acid reducers reduce the amount of acid produced by the stomach.
- Proton pump inhibitors also reduce the amount of acid produced by the stomach (and are generally more potent than histamine H2 acid reducers).
- Antacids neutralize stomach acid.
These treatments may be used in combination with other medications, especially if the ulcer is caused by an *H. pylori* infection.

**Medications to kill H. pylori bacteria**

Health professionals prescribe combination drug therapy to cure infection with *H. pylori* bacteria. Combination drug therapy usually includes at least 2 antibiotics, an acid reducer (which may include a proton pump inhibitor), and sometimes a bismuth compound.

**Medications to prevent ulcers**

Certain medications are used to protect the stomach from damage caused by frequent use of aspirin or other NSAIDs. These medications are called prostaglandin analogs (such as misoprostol). They are sometimes used to prevent ulcers.

*Sucralfate* also may be given to treat and prevent gastric and duodenal ulcers.

**5.3.1 Histamine H₂-Receptor Antagonists**

**5.3.1.1. Dosage**

The adult maximum daily dose for acute and maintenance therapy for peptic ulcer disease, esophagitis, gastroesophageal reflux disease (GERD), hypersecretory conditions, gastritis and duodenitis is based on the compendia, literature and package labeling.
a. **Acute Therapy**

The maximum daily dose for histamine H$_2$-receptor antagonists when prescribed as acute therapy is summarized in Table 1. Dosage regimens exceeding these maximum recommended values will be reviewed.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Histamine H$_2$-Receptor Antagonists</th>
<th>Adult Maximum Daily Acute Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRUG</td>
<td>MAXIMUM DOSE</td>
<td></td>
</tr>
<tr>
<td>Cimetidine (Tagamet®, generics)</td>
<td>duodenal ulcer: 1600 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gastric ulcer: 1200mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GERD: 1600 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypersecretory conditions: 2400mg/day</td>
<td></td>
</tr>
<tr>
<td>Famotidine (Pepcid®)</td>
<td>duodenal, gastric ulcer: 40 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GERD: 40 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypersecretory conditions: 640 mg/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>esophagitis: 80 mg/day</td>
<td></td>
</tr>
<tr>
<td>Nizatidine (Axid®)</td>
<td>duodenal, gastric ulcer: 300 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

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b. Maintenance Therapy

Maintenance dosages for available histamine H$_2$-receptor antagonists are summarized in Table 2. Dosage regimens exceeding maximum recommended values will be reviewed.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histamine H$_2$-Receptor Antagonists</strong></td>
</tr>
<tr>
<td><strong>Adult Maximum Daily Maintenance Dose</strong></td>
</tr>
<tr>
<td><strong>DRUG</strong></td>
</tr>
</tbody>
</table>
| Cimetidine | duodenal ulcer: 400 mg/day  
hypersecretory conditions: 2400mg/day |
| Famotidine | duodenal ulcer: 20 mg/day  
hypersecretory conditions: 640 mg/day |
Nizatidine  | duodenal ulcer: 150 mg/day
--- | ---
Ranitidine  | duodenal, gastric ulcer: 150 mg/day
  | hypersecretory conditions: 6 g/day
  | erosive esophagitis: 300 mg/day

### 5.3.1.2. Duration of Therapy

Clinical studies document a maximum treatment duration of 56 days (eight weeks) for anti-ulcer therapy in the treatment of acute peptic ulcer disease, gastritis and duodenitis. The Texas Vendor Drug Program limits reimbursement for $H_2$-receptor antagonists and related drugs to 62 days per calendar year at the maximum daily acute dose listed in Table 1. This treatment duration has been allotted to allow the usual 31 days supply per prescription. The prescribing physician may continue acute dosage regimens for periods longer than 62 days per calendar year for patients with conditions such as hypersecretory disease states, esophagitis, or gastroesophageal reflux disease (GERD). A diagnosis must be written on the prescription for acute treatment regimens exceeding the recommended treatment duration of 62 days per calendar year. Treatment regimens at acute dosage levels lasting longer than six months will be reviewed.

Maintenance therapy, at the recommended daily maintenance dose (Table 2), may be continued indefinitely based on patient need.

### 5.3.1.3 Duplicative Therapy
Pharmacotherapy of Peptic Ulcer and Prescription of Anti-Ulcer Drugs in various Diseases

The combination of two or more histamine H₂-receptor antagonists or a histamine H₂-receptor antagonist and misoprostol is not supported by the current literature. Therefore, concurrent use of these combinations will be reviewed as there is no clinical evidence to suggest that these adjunctive therapies improve outcome.

5.3.1.4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions.

The following drug-drug interactions are considered clinically relevant for anti-ulcer histamine H₂-receptor antagonists. Only those drug-drug interactions identified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed:

a. Warfarin and Cimetidine [clinical significance level - severe (First DataBank); 1 (DIF); 2 (Hansten & Horn)]

Interactions with warfarin are clinically significant as this compound possesses a narrow therapeutic index. The combined use of warfarin and cimetidine results in prolongation of prothrombin time and increased bleeding risk. Studies have documented that cimetidine inhibits the hepatic metabolism of warfarin. The cimetidine-warfarin interaction appears to be dose-related and is associated with considerable interpatient variability.
b. **Theophyllines and Cimetidine** [clinical significance level - severe (First DataBank); 2 (DIF); 3 (Hansten & Horn)]

Interactions with theophylline are clinically significant as this compound possesses a narrow therapeutic index. Cimetidine impairs theophylline metabolism when the two agents are administered concomitantly. Increased theophylline serum levels and theophylline toxicity have been reported following combined drug therapy with cimetidine and theophylline. Studies have shown that cimetidine interferes with the hepatic microsomal enzyme system which subsequently delays theophylline metabolism and elimination. Concurrent theophylline and cimetidine use could be considered appropriate if proper monitoring and/or dosage adjustments are made.

c. **Tacrine (Cognex) and Cimetidine** [clinical significance level - severe (First DataBank); 4 (DIF); 3 (Hansten & Horn)]

Concomitant administration of cimetidine and tacrine may result in enhanced pharmacologic effects of tacrine and the potential for tacrine toxicity. Cimetidine presumably inhibits the cytochrome P450 enzyme (P450 IA2) responsible for tacrine metabolism resulting in elevated serum tacrine concentrations. An alternative H₂-receptor antagonist should be considered when tacrine therapy is prescribed as this interaction is not expected with other available H₂-receptor antagonists. If cimetidine and tacrine are prescribed concurrently, monitor clinical response of the patient and adjust tacrine doses when necessary.
d. **Narcotic Analgesics and Cimetidine** [clinical significance level - severe (First DataBank); 4 (DIF); 3 (Hansten & Horn)]

Concurrent use of some narcotic analgesics and cimetidine may result in enhanced pharmacologic effects of narcotic analgesics. It is speculated that hepatic metabolism of certain narcotic analgesics may be inhibited by cimetidine, resulting in significant respiratory and/or central nervous system depression. Morphine undergoes glucuronidation rather than metabolism by the cytochrome P450 enzyme system and is minimally effected by adjunctive cimetidine administration. Other available H$_2$-receptor antagonists are less likely to interact than cimetidine and should be considered in patients prescribed narcotic analgesics. Patients receiving cimetidine concurrently with narcotic analgesics should be observed for signs and symptoms of enhanced respiratory and/or central nervous system depression.

e. **Itraconazole, Ketoconazole and H$_2$-Receptor Antagonists** [clinical significance level - severe (First DataBank); 2 (DIF); 3 (Hansten & Horn)]

Since oral itraconazole and ketoconazole absorption is dependent on an acidic environment, the combination of any H$_2$-receptor antagonist or proton pump inhibitor with these antifungal agents is considered to be problematic. H$_2$-receptor antagonists as well as proton pump inhibitors increase gastric pH and subsequently limit the absorption of itraconazole and ketoconazole. Observe patients routinely for reduced antifungal effect when any of these anti-ulcer agents are
administered concomitantly with either itraconazole or ketoconazole. The concurrent use of itraconazole or ketoconazole and H$_2$-receptor antagonists will be reviewed.

1. **Cimetidine and Dofetilide (Tikosyn7)** [clinical significance level - contraindicated (First DataBank); 1 (DIF); 3 (Hansten & Horn)]

Combined administration of cimetidine and dofetilide may result in increased serum levels and enhanced pharmacologic effects of dofetilide, including torsades de pointes. Cimetidine inhibits active tubular secretion of dofetilide, which has resulted in significant increases in dofetilide plasma concentrations. The manufacturer of dofetilide states that concurrent administration of dofetilide and cimetidine is contraindicated. Alternative medications that have no effect on dofetilide pharmacokinetics, such as omeprazole and ranitidine, should be considered as alternatives to cimetidine. The combined use of cimetidine and dofetilide is not recommended and will be reviewed.

### 5.3.2 Proton pump inhibitor

**INTRODUCTION**

Proton pump inhibitors have emerged as the agents of choice for the treatment of acid-related gastrointestinal disorders for many patients. These agents reduce gastric acid secretion and raise intragastric pH by inhibiting the final step of gastric acid production. Proton pump
inhibitors have been proven to be effective in the treatment of gastroesophageal reflux disease (GERD), duodenal ulcers, gastric ulcers, and pathologic hypersecretory conditions such as Zollinger-Ellison syndrome. Currently, five proton pump inhibitors are marketed: esomeprazole (Nexium®), lansoprazole (Prevacid®), omeprazole (generic, Prilosec®), pantoprazole (Protonix®), and rabeprazole (Aciphex®). This article will review the pharmacology of the proton pump inhibitors, identify similarities and differences between the specific agents, and discuss their use in acid-related gastrointestinal disorders.

**MECHANISM OF ACTION**

Proton pump inhibitors reduce gastric acid secretion from the gastric parietal cell through the inhibition of the gastric acid pump, H⁺/K⁺ ATPase. The gastric acid pump is located within the gastric parietal cell, and is also commonly referred to as the proton pump, hence the class name “proton pump inhibitors”. When the gastric parietal cell is activated, the gastric H⁺/K⁺ ATPase is translocated from the tubulovesicular membranes to the secretory canaliculus of the parietal cell. The gastric acid pump then begins exchanging potassium ions (K⁺) for hydrogen ions (H⁺). Simultaneously, chloride ions (Cl⁻) diffuse from the bloodstream into the parietal cell. H⁺ and Cl⁻ then combine to form hydrochloric acid (HCl).

The proton pump inhibitors are substituted 2-pyridyl methylsulfinyl benzimidazoles. These agents are protonatable weak bases that accumulate selectively within acidic environments with a pH < 4. Such an environment is found primarily in the secretory canaliculus,
the acidic compartment of the parietal cell. When protonated, the drug is converted to its active form, a tetracyclic sulfenamide. The sulfenamide binds covalently to the H⁺/K⁺ ATPase, rendering it inactive. The binding of the proton pump inhibitor to the gastric acid pump is irreversible and gastric acid secretion is inhibited in a dose-dependent manner. The proton pump inhibitors inhibit the gastric acid pump regardless of the stimulus for acid secretion.

**PHARMACODYNAMIC PROPERTIES**

The extent of mucosal damage and symptoms associated with acid-related gastrointestinal disorders are dependent upon gastric pH. The important role of gastric acid in these disorders is illustrated by the success of antisecretory therapy in treating these disorders. Mucosal healing has been directly correlated with the percentage of a 24-hour period that the intragastric pH remains above 4. Pharmacodynamic studies have focused on evaluating the degree of inhibition the proton pump inhibitors have on gastric acid secretion.

The antisecretory effect of the proton pump inhibitors begins within one to three hours after administration. The proton pump inhibitors result in a prolonged, sustained inhibition of gastric acid secretion, an unexpected pharmacodynamic action in view of their short pharmacokinetic half-life. The sustained inhibition is apparently a result of prolonged irreversible binding to the gastric acid pump. Secretory activity gradually returns to normal after discontinuation of therapy.
In pharmacodynamic studies, five days of treatment with esomeprazole 20 mg and 40 mg resulted in the intragastric pH remaining above 4 for a mean of 53% and 70%, respectively, of the monitored 24-hour period. Similarly, five days of therapy with lansoprazole 15 mg and 30 mg and eight days of therapy with rabeprazole 20 mg maintained the intragastric pH greater than 4 for a mean of 49%, 66%, and 60%, respectively, of the monitored 24-hour period. Multiple daily dosing of omeprazole 20 mg and 40 mg resulted in a decrease in the 24-hour intragastric acidity by 80 and 97%, respectively, and seven days of therapy with pantoprazole 40 mg decreased intragastric acid secretion by 85%.

The effect of proton pump inhibitors is selective for gastric acid secretion. In studies evaluating the effect of proton pump inhibitors on circulating hormone levels, no apparent effect was noted on the following hormones: cortisol, testosterone, estradiol, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

**PHARMACOKINETIC PROPERTIES**

The stability of the proton pump inhibitors is dependent upon pH. They are rapidly degraded in acid media and available formulations, which include enteric-coated tablets or capsules containing enteric-coated granules, have been formulated to protect the drug from the acidity of the stomach. The enteric coating protects the drug from
harmful stomach acid, dissolving after the medication has passed through the acidic stomach and into a more alkaline environment.

The proton pump inhibitors are rapidly absorbed after oral administration, with peak plasma concentrations (Cmax) occurring within 0.5 to 5 hours after administration. The Cmax and area under the serum concentration time curve (AUC) increase in a dose-dependent manner following single dose administration of the proton pump inhibitors. The absolute bioavailability of lansoprazole, pantoprazole, and rabeprazole is > 80%, 77%, and 52%, respectively. Omeprazole has an absolute bioavailability of 30 to 40% after a single dose, which increases slightly with repeated administration. Similarly, the absolute bioavailability of esomeprazole is 64% after a single dose, and increases to 90% with multiple dosing. Esomeprazole differs from other proton pump inhibitors in that it is the first proton pump inhibitor developed as a single optical isomer. It consists of only the S-isomer of omeprazole. The pharmacokinetics of lansoprazole, pantoprazole, and rabeprazole are unaffected by multiple dosing. The proton pump inhibitors are highly protein bound (95-98%) and have short plasma half-lives ranging from 0.5 to 2 hours.

The Cmax and AUC of lansoprazole, esomeprazole, and omeprazole are diminished when administered after food intake. Although the administration of pantoprazole or rabeprazole with food may delay their absorption by 4 hours or longer, the Cmax and AUC are unaffected. Thus, pantoprazole and rabeprazole may be administered without regard to meals, whereas it is recommended
that lansoprazole, esomeprazole, and omeprazole be administered before a meal.

Proton pump inhibitors undergo extensive hepatic metabolism by the cytochrome (CYP) P450 isoenzyme system, primarily by the isoenzymes 2C19 and 3A4. Metabolites lack significant antisecretory activity. The majority of the dose (67-90%) is eliminated as inactive metabolites in the urine, with the remainder of the dose excreted as inactive metabolites in the feces. Very little to no active drug is excreted unchanged in the urine.

**USE IN SPECIAL POPULATIONS**

The pharmacokinetics of the proton pump inhibitors have been evaluated in patients with renal or hepatic insufficiency. Pharmacokinetics are not expected to be altered in patients with renal insufficiency, and no dosage adjustments are necessary in renal impairment. This is supported by pharmacokinetic studies showing similar parameters between healthy subjects and those with renal impairment. In contrast, proton pump inhibitors are significantly metabolized through the hepatic system, and therefore have the potential to accumulate in those with hepatic impairment. Pharmacokinetic studies of patients with hepatic disease have displayed increases in half-life and AUC. No dosage adjustments are necessary in patients with mild to moderate hepatic insufficiency; however, dosage adjustments should be considered in patients with severe hepatic insufficiency. For example, the manufacturer’s product information for esomeprazole recommends using no more than 20 mg per day in patients with severe hepatic disease.
Dosage adjustments are not necessary in elderly patients, and only slight to moderate increases in AUC (25-50%) and Cmax (18-60%) have been reported. In female patients, studies of pantoprazole and esomeprazole have shown slight increases in the AUC and Cmax, but these differences were not clinically relevant. In addition, studies of lansoprazole found no gender differences in intragastric pH results. No dosage adjustments are necessary based upon gender.

The pharmacokinetics of lansoprazole have been evaluated in pediatric patients, aged 1 to 11, with doses of 15 mg daily in patients weighing £ 30 kg and 30 mg daily in patients > 30 kg. The mean Cmax and AUC were similar between pediatric patients and healthy adult subjects. Per manufacturer’s product information, the safety and effectiveness of the remaining proton pump inhibitors have not been established in patients less than 18 years of age. A MEDLINE/Pubmed search identified studies evaluating the safety and effectiveness of omeprazole in over 200 patients aged 1 to 18. These studies concluded that omeprazole was well-tolerated, effective, and safe in pediatric patients.

The CYP2C19 isoenzyme displays a known genetic polymorphism with 3% of Caucasians and African-Americans and approximately 20% of Asians having a deficiency of this isoenzyme. These subpopulations metabolize agents through CYP2C19 slowly, and are therefore termed “poor metabolizers.” Pharmacokinetic studies have shown moderate (2- to 4-fold) increases in the AUC of poor metabolizers, and studies of pantoprazole revealed minimal accumulation (< 23%) with daily dosing in this subpopulation.
THERAPEUTIC USES

Proton pump inhibitors are used for the treatment of various gastrointestinal disorders, including GERD, duodenal ulcers, gastric ulcers, H. pylori, and pathologic hypersecretory conditions such as Zollinger-Ellison syndrome.

Gastroesophageal Reflux Disease: More than 60 million people in the United States are affected by GERD, and more than 25 million of these suffer from heartburn daily. GERD may significantly affect a patient’s normal daily activities, though it is rarely life threatening. GERD is characterized by prolonged and repeated exposure of the esophageal mucosa to acidic gastric contents due to a failure of the esophageal sphincter in preventing reflux. Prolonged or repeated exposure may ultimately result in erosive or ulcerative damage to the esophagus, termed erosive esophagitis. Multiple mechanisms may be responsible for the development of GERD; these include but are not limited to, transient relaxation of the lower esophageal sphincter, increased intra-abdominal pressure, gastric distension, peptides, hormones, various foods, and medications. The spectrum and intensity of symptoms associated with GERD vary drastically among patients.

The American College of Gastroenterology has developed guidelines regarding the treatment of GERD. These guidelines emphasize acid suppression as the mainstay of therapy. Proton pump inhibitors have been proven to provide rapid symptomatic relief and to result in the healing of erosive esophagitis. Histamine-2 receptor blockers are also effective; however, proton pump inhibitors eliminate symptoms more
quickly and heal erosive esophagitis more frequently and rapidly. Because both classes of agents are effective, there is ongoing debate regarding the appropriate initial treatment for GERD. Some clinicians prefer to utilize a “step-up” approach to therapy, in which therapy is initiated with a histamine-2 receptor blocker and titrated up to a proton pump inhibitor if symptom relief or healing does not occur. Other clinicians prefer a “step-down” approach, beginning with a proton pump inhibitor and decreasing to the therapy that provides the lowest amount of acid suppression while maintaining control of symptoms. To date, neither approach has proven superior, so the choice of therapy is left up to the individual provider and patient.

Each of the currently available proton pump inhibitors has FDA approved indications for the symptomatic treatment of GERD, for the healing and symptomatic resolution of erosive esophagitis, and for the maintenance of healing of erosive esophagitis.

**H. pylori, Gastric Ulcer, and Duodenal Ulcer:** H. pylori is a spiral, motile, gram-negative organism which causes gastritis, an inflammatory response in the wall of the gastric mucosa, in many of those infected. H. pylori is now recognized as the single most common cause of peptic ulcer, and has been implicated as a risk factor for gastric adenocarcinoma and low grade gastric lymphoma of mucosa-associated lymphoid tissue (MALT). Successful eradication of H. pylori in infected individuals has been shown to heal ulcer disease and prevent relapse in a majority of patients. The American College of Gastroenterology recommends that all ulcer patients with H. pylori infection be treated.
Currently, esomeprazole, lansoprazole, omeprazole, and rabeprazole based dual- or triple-drug regimens have received FDA approval for the eradication of H. pylori. Concomitant therapy with a proton pump inhibitor plus an antimicrobial agent, specifically clarithromycin and/or amoxicillin, for 7 to 14 days is commonly used for H. pylori eradication. Combination therapy is essential to maximize eradication and to minimize the risk of resistance. With combination therapy, the proton pump inhibitors increase gastric pH, allowing greater organism growth, and thus increasing the susceptibility of H. pylori to antimicrobial therapy.

An effective combination regimen that has a high eradication rate should be used. Triple-drug regimens typically yield higher eradication rates than dual-drug regimens. Triple-drug therapy with omeprazole has produced eradication rates of 77 to 90%, while dual-drug therapy produced rates of 64 to 83%. Similarly, triple-drug therapy with lansoprazole yielded eradication rates of 85 to 92%, versus 66 to 77% with dual-drug therapy. Triple-drug therapy with rabeprazole and esomeprazole has produced eradication rates of 84-86%.

Peptic ulcer disease is commonly attributable to either H. pylori infection or use of nonsteroidal anti-inflammatory drugs (NSAIDs). Most patients with peptic ulcer disease who are not taking NSAIDs will have evidence of H. pylori infection. Because the eradication of H. pylori facilitates healing of ulcers and reduces rates of recurrence, the American College of Gastroenterology recommends testing for H. pylori infection in all patients with peptic ulcer disease. Patients that
are infected with H. pylori should receive appropriate treatment for eradication. In addition, all patients with peptic ulcer disease should be evaluated for NSAID use. NSAIDs are commonly prescribed agents, and their availability over-the-counter further contributes to their widespread use. For patients with peptic ulcer disease, NSAID use should be discontinued if possible.

Lansoprazole and omeprazole are FDA approved for the treatment of active duodenal and gastric ulcers, with lansoprazole also having an indication for the maintenance of healing of duodenal ulcer. Rabeprazole is also indicated for the treatment of active duodenal ulcer. These agents have been shown to provide similar healing rates and symptom relief in the treatment of peptic ulcer disease. Healing of duodenal ulcers with proton pump inhibitor therapy typically occurs within four weeks. However, some patients may require an extra course of therapy to allow for healing.

Lansoprazole also has FDA approved indications for the treatment of NSAID-associated gastric ulcer in patients who continue NSAID use and for reducing the risk of NSAID-associated gastric ulcers in patients with a history of gastric ulcer who require the use of an NSAID. Lansoprazole should be dosed at 30 mg daily for the treatment of a NSAID-associated gastric ulcer and at 15 mg daily for reducing the risk of NSAID-associated gastric ulcers.
Pathologic Hypersecretory Conditions: Long-term treatment with lansoprazole, omeprazole, pantoprazole, and rabeprazole is effective in the management of pathological hypersecretory conditions such as Zollinger Ellison syndrome. Zollinger Ellison syndrome is caused by a gastrin-producing tumor of the pancreas or duodenum, termed gastrinoma. These gastrinomas result in an overproduction of stomach acid which may lead to the development of multiple, intractable ulcers in the duodenum and other areas of the small bowel. Patients often experience abdominal pain and diarrhea.

Treatment is aimed at controlling acid hypersecretion and possible surgical removal of the gastrinoma. Because of their ability to successfully suppress acid production and promote ulcer healing, the proton pump inhibitors are first line agents for this condition and dramatically reduce associated complications.

The results of several studies involving over 240 patients have shown these agents significantly inhibit gastric acid secretion and control associated symptoms including diarrhea, anorexia, and pain. In clinical studies, the initial daily dose of the proton pump inhibitor was titrated individually to maintain gastric acid output below 10 mEq/hr in patients without prior acid-reducing surgery and below 5 mEq/hr in patients with prior acid-reducing surgery. Effective dose ranges varied significantly with the following found to be effective: 15 mg every other day to 180 mg daily of lansoprazole, 20 mg every other day to 360 mg daily of omeprazole, 80 mg to 240 mg daily of pantoprazole, and 20 mg to 120 mg daily of rabeprazole. Treatment with rabeprazole has been studied for up to 12 months, while studies
of pantoprazole, lansoprazole, and omeprazole have extended greater than two, four, and five years, respectively. In addition, acid secretion was maintained below the target level ($\leq 10$ mEq/hr) in 35 patients treated with 160 mg or 240 mg per day of intravenous pantoprazole for six days. High doses of these proton pump inhibitors have been well tolerated for prolonged periods.

**DRUG INTERACTIONS**

The proton pump inhibitors are extensively metabolized by the CYP450 isoenzyme system. Clinically significant interactions may occur with other drugs metabolized through this system. Drug-drug interactions vary based upon the individual proton pump inhibitor.

Lansoprazole causes a minor increase (10%) in the clearance of theophylline. Although this interaction is unlikely to be clinically relevant, some patients may require theophylline dosage adjustments. Esomeprazole has been shown to cause a 45% decrease in the clearance of diazepam. Plasma levels of diazepam were increased 12 hours and beyond, however, the interaction is unlikely to be clinically significant. No other clinically significant interactions with drugs metabolized by the CYP450 isoenzyme system are expected with lansoprazole or esomeprazole.

Omeprazole may prolong the elimination of phenytoin, diazepam, and warfarin, and may interact with other drugs metabolized through the CYP450 isoenzyme system.

Pantoprazole and rabeprazole have not shown any clinically significant interactions with other drugs metabolized through the
CYP450 system. Therefore, co-administration of these agents with drugs having the same metabolic pathways are not expected to require dosage adjustments.

Concomitant administration of the proton pump inhibitors and warfarin has been associated with International Normalized Ratio (INR) increases. Because increases in the INR may result in abnormal bleeding and complications, patients may need to be monitored more closely when treatment is initiated or modified.

Co-administration of the proton pump inhibitors with antacids has produced no clinically relevant interactions. Proton pump inhibitors may interfere with the absorption of drugs in which gastric pH is an important determinant of bioavailability. Examples of such drugs include ketoconazole, ampicillin esters, iron salts, and digoxin. Careful monitoring is recommended for all potentially significant drug interactions with proton pump inhibitors.

ADVERSE EFFECTS

The proton pump inhibitors are generally well tolerated. The most commonly reported adverse effects in both short-term and long-term clinical trials have been headache, diarrhea, nausea, and abdominal pain.

The profound decrease in gastric acid secretion by the proton pump inhibitors leads to an increase in gastrin production and sustained increases (3- to 4- fold) in serum gastrin levels. There has been concern that hypergastrinemia may promote enterochromaffin-like
(ECL) cell hyperplasia, gastric carcinoma, and adenocarcinoma. A clinical study of gastric corpus biopsy specimens of patients that received omeprazole therapy for up to 11 years revealed only minimal metaplasia and no neoplasia or dysplasia. The American College of Gastroenterology states that the potential benefit of long-term proton pump inhibitor therapy in patients with chronic or complicated GERD outweighs any theoretical risk. Therefore, elevated gastrin levels are considered to be of minimal clinical relevance and measurement of plasma gastrin levels is unnecessary.

USE IN PREGNANCY & LACTATION

With the exception of omeprazole, the proton pump inhibitors are classified as Pregnancy Category B. For those agents classified as pregnancy category B, studies in rats and rabbits have not revealed evidence of impaired fertility or harm to the fetus. There are, however, no well-controlled studies in pregnant women and these drugs should be used only if clearly needed. Omeprazole is classified as Pregnancy Category C. Omeprazole studies in rabbits, dosed at 17 to 172 times the human dose, and in rats, dosed at 35 to 345 times the human dose, produced dose-related fetal toxicity. There have been sporadic reports of congenital abnormalities in babies born to mothers who received omeprazole during pregnancy.

It is not known whether or not proton pump inhibitors are excreted in human milk. Drugs that are excreted in human milk may potentially result in serious adverse reactions in nursing infants. Therefore, because of the potential for a serious adverse reaction, a decision
should be made to either discontinue nursing or to discontinue the drug.

**AVAILABILITY**

The proton pump inhibitors are available in various formulations that protect the agents from stomach acidity. Rabeprazole and pantoprazole are available as enteric-coated tablets, while esomeprazole, omeprazole, and lansoprazole are available as delayed-release capsules containing enteric-coated granules. Patients should be instructed that these medications should not be crushed or chewed, but should be swallowed whole. For patients with difficulty swallowing, the esomeprazole, lansoprazole, or omeprazole capsules may be opened and the granules sprinkled into applesauce, then swallowed immediately. Lansoprazole has also been shown to remain effective if mixed with apple juice, orange juice, tomato juice, cottage cheese, yogurt, or strained pears. Lansoprazole is also available as orally disintegrating tablets known as Prevacid SoluTabs®. These tablets should be placed on the tongue. The tablet will disintegrate within one minute, then the granules can be swallowed. For patients with a nasogastric tube, lansoprazole capsules may be opened, mixed with apple juice and administered through the nasogastric tube. Although all proton pump inhibitors are available in various formulations for oral delivery, pantoprazole is the only proton pump inhibitor that is currently available for intravenous administration.

**CONCLUSION**

Pharmacists are often the initial contact for patients with
gastrointestinal disorders. This will increase even more with omeprazole’s anticipated over-the-counter availability later in 2003. Other proton pump inhibitors, as with histamine-2 receptor blockers, will likely follow this trend. An understanding of appropriate therapy and the available options is imperative for pharmacists making both recommendations and referrals. The proton pump inhibitors have proven to be safe and effective in a wide array of acid-related gastrointestinal disorders. The proton pump inhibitors display many similarities, including their ability to profoundly decrease gastric acid production. They have demonstrated superiority to histamine-2 receptor blockers for the treatment of acid-related gastrointestinal disorders in many patients. The proton pump inhibitors are well tolerated, even when given in high doses such as those used for treating pathological hypersecretory conditions. The widespread utilization of the proton pump inhibitors will continue to provide major benefit for the many patients with acid-related gastrointestinal disorders.

5.3.3 MISOPROTOL

Mechanism
Gastric Mucosa Protection by prostaglandin replacement

Preparations
Misoprostol (Cytotec)

Indication
Peptic Ulcer Disease prevention
Prevents ulcers in those on NSAIDs chronically

**Cervical Ripening** agent in Pregnancy **Labor Induction**

**Dosing**

See **Cervical Ripening** for pregnancy dosing

Option 1: 100 ug qid with food

Option 2: 200 ug bid with food

Better tolerated than qid dosing

**Side Effects**

**Diarrhea**

Poorly tolerated

**Efficacy:** **Peptic Ulcer Disease** reduction

Dosing qid: 4% **Peptic Ulcer Disease** recurrence

Dosing bid: 8% **Peptic Ulcer Disease** recurrence

**Placebo:** 16% **Peptic Ulcer Disease** recurrence

**5.3.4 ANTACID**

Antacids act by neutralizing gastric acid and thus raising the gastric pH. This is the effect of inhibiting peptic activity, which practically ceases at pH 5. Given in sufficient quantity for long enough they can produce healing of duodenal ulcers but are less effective for gastric ulcers.

The antacids in common use are salts of magnesium and aluminium. Magnesium salts cause diarrhoea and aluminium salts
constipation, so mixtures of these two can be used to preserve normal bowel function.
Some preparation of these substances (e.g. magnesium trisilicate mixture and some proprietary aluminium preparations) contain high concentrations of sodium and should not be given to patients on a sodium-restricted diet.

Numerous antacid preparations are available; a few of the main ones are given below.

- **Magnesium hydroxide** is an insoluble powder that forms magnesium chloride in the stomach. It does not produce systemic alkalosis since magnesium ion is poorly absorbed from the gut.
- **Magnesium trisilicate** is an insoluble powder which reacts slowly with the gastric juice forming magnesium chloride and colloidal silica. This agent has a prolonged antacid effect, and it also adsorbs pepsin.
- **Aluminium hydroxide** gel forms aluminium chloride in the stomach; when this reaches the intestine the chloride us released and is reabsorbed. Aluminium hydroxide raises the pH of the gastric juice to about 4; it also adsorbs pepsin. It acts gradually and its effect continues for several hours. Collodial aluminium hydroxide combines with phosphates in the gastrointestinal tract and the increased excretion of phosphate in the faeces which occurs results in decreased excretion of phosphate via the kidney. This is important in the management of patients with chronic renal failure.
- **Sodium Bicarbonate** acts rapidly and is said to raise the pH of gastric juice to about 7.4. Carbon dioxide is liberated and this causes
belching. The co2 stimulates gastrin secretion and can result in a secondary rise in acid secretion. Since some sodium bicarbonate is absorbed in the intestine, large doses or frequent administration of this antacid can cause alkalosis, the onset of which can be insidious. This agent should therefore not be prescribed for long-term treatment; nor should it be given to patients who are on a sodium restricted diet.

- Alginates are sometimes combined with antacids for use in reflux oesophagitis, because they are believed to increase adherence of mucus to the oesophageal mucosa.

### 5.3.5 Prevention

One can greatly reduce the chance that to develop a peptic ulcer if:

**Don't start smoking.** If one smoke, quit. Smokers are much more likely to develop ulcers than nonsmokers.

**Avoid taking certain medications.** Avoid aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs). If one must take these medications regularly, take the smallest possible dose, and always take them with food. In many people, newer NSAIDs such as the COX-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex) reduce inflammation and pain
without causing as much gastrointestinal damage as other NSAIDs. Some NSAIDs are made with a coating (called an enteric coating) that reduces the amount of stomach irritation they cause. However, the coating does not eliminate the risk of developing an ulcer if these medications are used frequently. Check with doctor before changing the medications.

**Drink alcoholic beverages only in moderation.** Never drink alcohol on an empty stomach.

**References**


Pharmacotherapy of Peptic Ulcer and Prescription of AntiUlcer Drugs in various Diseases


20. Drug Information Service, The University of Texas Health Science Center at San Antonio, and the College of Pharmacy, The University of Texas at Austin.


