Section 3

LECTURE

Gastroduodenal Pathophysiology and Disorders

Gastroduodenal Pathophysiology

and

Disorders

Gastric Acid Secretion

Parietal cells, which are located in the oxyntic glands of the body and fundus of the stomach, secrete acid via an active, energy-dependent process. Secretion of acid follows a circadian pattern with the lowest amounts produced in the morning and the highest amounts in the evening. The normal basal acid output (BAO) is typically less than 5 meq/hr, although there can be considerable variation among normal subjects due to differences in parietal cell mass. Vagal tone and local histamine release appear to be the main factors in basal acid output.

The principal physiologic stimulant of acid secretion is food. Meal-stimulated acid secretion occurs in three phases. The cephalic phase refers to stimulation of acid secretion by the sight, smell, thought, and taste of food. Each of these leads to parietal cell stimulation via cholinergic input through the vagus nerve. Vagotomy completely abolishes this response. When food enters the stomach, the gastric phase of acid secretion is activated. Distention of the stomach leads to partial cell stimulation via neural pathways (vagal and intramural) and via secretion of gastrin. Release of gastrin is

also triggered by the presence of nutrients, especially amino acids, in the antrum. Gastrin release and increased acid secretion occurs with coffee (including decaffeinated), alcohol, milk, and soft drinks. The intestinal phase of acid secretion occurs when nutrients pass from the stomach into the intestines. The exact mediators for this phase have not been fully elucidated.

Hydrogen ions are secreted by parietal cells into the gastric lumen against a tremendous concentration gradient (3 million-to-1). Chloride ion secretion also occurs against a concentration gradient as well as an electrical gradient. The secretion of acid by the parietal cell requires energy for active transport. This process is a result of activation of a unique proton pump, the H^+, K^+ - ATPase pump. This pump is a magnesium-dependent enzyme found only in secretory (apical and tubulovesicular) membranes of parietal cells. The proton pump is distinct from the Na^+, K^+ - ATPase pump present in all cells of the body in that it is not inhibited by ouabain. The proton pump secretes one hydrogen ion from the cytoplasm of the parietal cell in exchange for one potassium ion from the lumen of the secretory canalicular. During the non-stimulated resting state, the pumps appear to be localized primarily to tubulovesicles in the cytoplasm of the parietal cell. During the stimulated secretory state, the pumps move from the tubulovesicular location to the apical secretory canalicular membrane, which becomes greatly expanded. The tubulovesicles either fuse with the apical membrane (membrane recycling hypothesis) or they may in fact be confluent with the apical surface via a collapsed compartment which expands osmotically upon parietal cell stimulation (osmotic flow hypothesis). The apical membrane also contains conductance pathways for secretion of

chloride ions and potassium ions from the parietal cell into the lumen. These conductance pathways may not be operational in the unstimulated state.

The basolateral membrane of the parietal cell contains numerous receptors, including those for histamine, gastrin, and acetylcholine. Histamine is released from the enterochromaffin cells in the body and fundus of the stomach. Histamine traverses intercellular spaces to bind to the H_2 receptors on the basolateral membrane of the parietal cell (paracrine stimulation). Binding to the H_2 receptor activates adenylate cyclase converting cytosolic ATP to cyclic AMP. The H_2 receptor is coupled to a stimulatory GTP-binding protein (Gs), which is responsible for activation of adenylate cyclase. The cyclic AMP generated stimulates protein kinases that phosphorylate cellular proteins, which ultimately results in activation of the H^+, K^+-ATPase pump and acid secretion.

Gastrin is released into the blood stream by the antral G-cells, thus it acts as a hormone (endocrine stimulation). Gastrin binds to its receptor on the basolateral membrane of the parietal cell, which is coupled to phospholipase C via a GTP-binding protein. Phospholipase C catalyzes the breakdown of membrane phospholipids to inositol triphosphate (IP_3), which releases calcium from intracellular stores. Acetylcholine is released from postganglionic, parasympathetic neurons in response to vagal stimulation (neurocrine stimulation). Acetylcholine binds to the parietal cell via a muscarinic (M_3) cholinergic receptor. Binding to the M_3 receptor is coupled to phospholipase C via a GTP-binding protein. Release of calcium from intracellular stores activates the H^+, K^+-ATPase pump resulting in the secretion of acid. Gastrin and

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acetylcholine may also influence acid secretion by stimulating histamine release from ECL cells.

The receptors on the basolateral membrane can be inhibited by receptor antagonists (for example, H_2 receptor antagonosts or anti-cholinergic agents) or by surgical vagotomy (acetycholine) or antrectomy (gastrin). The H^+, K^+-ATPase pump can be inhibited by proton pump inhibitors (PPIs), such as omeprazole or lansoprazole. PPIs form an irreversible, covalent bond with sulfhydryl groups of two cysteine residues of the alpha subunit of the H^+, K^+-ATPase. The pump is prevented from exchanging H^+ and K^+ ions until new alpha subunits are synthesized and incorporated into the apical secretory canalicular membrane, which typically requires 24 hours to complete. Because the H^+, K^+-ATPase pump is the final common pathway in acid secretion, acid production is prevented regardless of the degree of parietal cell stimulation via gastrin, histamine or acetycholine.

Physiologic regulation of acid secretion is provided via a negative feedback inhibitory loop. As the gastric luminal pH becomes more acidic, further secretion of acid is down regulated. When the pH falls below 2.5 to 3.0, gastrin release from the antral G-cells is inhibited. In addition, gastric acidity stimulates production of somatostatin from D-cells in the antrum. Somatostatin has a paracrine influence on the G-cell resulting in diminished gastrin release, which in turn leads to decreased parietal cell secretion of acid. Somatostatin also binds to the parietal cell via a membrane receptor on the basolateral surface. Receptor binding decreases the level of cyclic AMP within the parietal cell by

coupled inhibition of adenylate cyclase via an inhibitory GTP-binding (Gi) protein. Prostaglandins decrease acid secretion via this same mechanism.

Pepsin Secretion

Pepsins are responsible for approximately 15% of dietary protein digestion. This proteolytic enzyme is secreted by the chief cells as well as the mucus gland cells in the form of pepsinogen, an inactive precursor. Pepsinogen secretion is apparently regulated by the same stimuli as in acid secretion. Acidic pH (<3.5) is required to activate pepsinogens to pepsin. Pepsinogens are irreversibly destroyed at a pH greater than 6. Pepsinogen activation and inactivation plays a role in the development of and the ability to heal peptic ulcer disease, respectively. However, their precise role in peptic ulcer disease remains to be further characterized.

Gastric Mucosal Defense

The gastric mucosa is continuously exposed to high concentrations of acid and other potentially injurious substances, thus effective mechanisms for maintenance of mucosal integrity must be intact. If the gastric mucosal defense mechanisms are deficient or impaired, or if the noxious agents are too strong, mucosal damage will occur.

At the level of the mucosa, the first line of protection is provided by mucus secretion by the surface mucus cells. These cells also secrete bicarbonate, which in combination with mucus, forms a physical and chemical barrier. The factors that stimulate acid and pepsin secretion appear to regulate bicarbonate and mucus production.

Bicarbonate is essential in establishing a pH gradient such that a neutral pH is maintained at the cell surface. The surface barrier exists as a gel containing an unstirred layer of mucus, bicarbonate, high molecular weight glycoproteins, water, and surface phospholipids. This gel layer is thin ($\sim 200\mu m$), impermeable to larger molecules, and has a diffusion coefficient for hydrogen ion 3-4 times smaller than water. It is susceptible to proteolytic damage by pepsin and it is damaged by aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), bile salts, and alcohol. Secretion of mucus and bicarbonate also occurs in the duodenum. In fact, the amount of bicarbonate secreted in the proximal duodenum is nearly twice the amount produced by the entire stomach.

Prostaglandins play an important role in mucosal cytoprotection, especially prostaglandin E_2. Prostaglandins are synthesized from the metabolism of arachidonic acid by the enzyme cyclooxygenase (COX). Prostaglandins are active mediators of inflammation but are also vital in the normal physiological functioning in a wide variety of tissues. In the stomach, normal prostaglandin synthesis is critical for mucus and bicarbonate secretion, mucosal blood flow to prevent hydrogen ion back diffusion, mucosal cellular repair and re-epithelialization, and maintenance of surface-active phospholipid layer. At high concentrations, prostaglandins inhibit acid secretion from the parietal cell. Aspirin and other NSAIDs are damaging to the GI tract mucosa because of their inhibition of cyclooxygenase and therefore prostaglandin production. There are two isoforms of cyclooxygenase, COX-1 and COX-2. They have a similar size (70 KD), enzyme kinetics, and amino acid sequence (75% homology). However, they are located on different chromosomes (chromosome 9 for COX-1; chromosome 1 for COX-2) and

they are thought to serve distinct tissue function. COX-1 is uniformly expressed on the endoplasmic reticulum membrane of all cells. COX-1 is critical in the normal physiologic functions in many tissues, including cytoprotection in the stomach. On the other hand, COX-2 has limited expression in the absence of inflammation. There is some routine expression of COX-2 in the brain, kidney, reproductive system, and to a lesser extent the GI tract and heart. The major role of COX-2 is in the mediation of inflammation. COX-2 is rapidly induced (within hours) in response to cytokines, growth factors, tumor necrosis factor, and other inflammatory mediators. All NSAIDs differ in their relative inhibition of COX-1 and COX-2. Specific COX-2 inhibitors have been developed in the hope of inhibiting the inflammatory effects of the COX-2 pathway prostaglandins, while not inhibiting the COX-1 prostaglandins important to normal physiologic function throughout the body. Large, multi-center phase III trials are investigating whether these specific COX-2 inhibitory NSAIDs have a better side effect and safety profile than non-selective NSAIDs while maintaining clinical anti-inflammatory efficacy.

Gastritis

Gastritis is defined as inflammation of the stomach, or more specifically, of the gastric mucosa. Despite the diverse etiologies of gastritis, the gastric mucosa has only a limited range of histologic responses which appear as stereotyped changes with little to help differentiate as to the causative etiology. Classification systems for gastritis have been hampered by these limitations. However, the most common classification system is

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the one developed in Sydney, Australia in 1990 and thus known as the Sydney System. Slight modifications were made in 1994 during the international workshop in Houston.

Histologic features of chronic gastritis are readily apparent on routine H & E stains of biopsy specimens. Mucosal atrophy with a decrease in the size or number of glands may be seen. Mononuclear cell inflammation in the lamina propria with formation of lymphoid follicles occurs with more severe injury. If the mononuclear inflammation is confined to the surface-foveolar zone, the term "chronic superficial gastritis" is often used. When neutrophils are identified in the surface epithelium or lamina propria, the term "active" gastritis is used. Neutrophils imply active inflammation, which may be acute or chronic in nature. Histology may also reveal the presence of goblet cells, absorptive cells, and Paneth cells. These are normal components of the small intestine but not the stomach, thus the term "intestinal metaplasia."

Helicobacter pylori gastritis. Gastric mucosal infection with *Helicobacter pylori* is the most common cause of chronic active gastritis. The recognition that an infection of the stomach was associated with chronic gastritis and peptic ulcer disease was first described in 1984 by Marshall and Warren. Marshall proved Koch's postulates by ingesting cultured isolates and developing active gastritis. Since the initial description, tremendous investigation and research have revolutionized the way gastritis, peptic ulcer disease, and even gastric malignancies are managed.

Helicobacter pylori is a gram-negative, spiral-shaped, microaerophilic, flagellated bacterium. The organism is found throughout the world; in fact, it is estimated 60% of

the world's population is infected. Humans are the only known host reservoir for H. pylori. Transmission of infection appears to be person-to-person although it is unclear whether this occurs via a fecal-oral or oral-oral route. The prevalence of infection and the age of acquisition varies tremendously between developed and underdeveloped regions of the world. In the U.S. approximately 30% of adults are infected; whereas, in some regions of the world, 80% of children have acquired the infection. In the U.S. early age of acquisition is associated with crowded living conditions, poor sanitation, low socioeconomic status, certain ethnic populations, and the presence of an infected family member, especially a parent. Higher rates of infection are seen in orphanages, mental institutions, and in health care employees. Geographic prevalence and age of acquisition likely explain the wide variation in distribution and prevalence of gastric malignancies.

The acidic environment of the stomach was originally felt to be an uninhabitable environment for bacteria, thus the strong skepticism at the time of the discovery of H. pylori. In order for it to survive, the H. pylori bacterium has several features to avoid or neutralize acid destruction. Flagella allow it to penetrate the protective mucus layer. Bacterial adhesins give it the ability to firmly attach to gastric mucosa. H. pylori produces an enzyme, urease, which converts urea to ammonia. This "ammonium cloud" creates a local alkaline environment around itself. Bacterial internalization and cellular invasion have been reported but are not thought to be a common pathogenic feature. H. pylori infection elicits a strong immunologic response, both cellular and antibody-mediated, which contribute to the mucosal damage. Unfortunately, the host immune response is not sufficient to eradicate the infection. Other bacterial virulence factors

include cytotoxins (cag A, vac A) which induce tissue inflammation; lipopolysaccharide which inhibits mucin synthesis; interleukins (IL-1, IL-8) which leads to neutrophil recruitment and activation; tumor necrosis factor which alters microvascular permeability; and catalase which generates oxygen free radicals. Damage to the mucus gel layer facilitates back diffusion of hydrogen ions potentiating gastric epithelial damage.

Acid secretion by parietal cells is altered by infection with H. pylori. During the acute phase of infection, nearly all patients experience a period of marked acid reduction or achlorhydria. Some patients will not recover acid secreting function; these patients are thought to be more prone to the subsequent development of gastric cancer. Most people with H. pylori infection will recover normal levels of acid production. Yet others will develop excess acid secretion in response to H. pylori infection. These latter patients have been found to have an elevated serum gastrin level or an exaggerated acid secretion to normal levels of gastrin stimulation. The exact mechanisms for altered gastrin responses or gastrin hypersecretion are not clear. Suggested hypotheses include the ammonia-generated alkaline environment in the vicinity of the antral G-cells or gastrin hypersecretion induced by inflammatory mediators. People infected with H. pylori have also been shown to have decreased numbers of antral D-cells with decreased mucosal somatostatin concentrations, which may contribute to the alterations in gastrin levels. Other studies have shown H. pylori infection diminishes bicarbonate secretion from the proximal duodenum. These alterations induced by H. pylori play a major role in the pathophysiology of peptic ulcer disease.

The natural history of H. pylori infection is interesting in that most people are completely asymptomatic and unaware of their infection. However, virtually everyone infected has histologic evidence of chronic active gastritis. Spontaneous clearance of the bacteria is rare; the overwhelming majority have a chronic, lifelong infection. Some patients will have a progression from chronic superficial gastritis to chronic atrophic gastritis. Those with chronic atrophic gastritis have a higher risk of progression to intestinal metaplasia , dysplasia, and gastric cancer. The lifetime risk of gastric cancer associated with H. pylori infection is 1-3%. One of six patients will develop peptic ulcer disease. Gastric lymphoma, especially the low-grade B cell mucosal-associated lymphoid type (MALT), has been linked to chronic H. pylori infection. Antibiotic eradication has been reported as a treatment for superficial MALT lymphoma, thus eliminating the need for aggressive surgical, chemotherapeutic , or radiation therapy.

Numerous diagnostic tests are available for detection of H. pylori infection. The most common non-invasive tests include serologic and breath testing. Serology utilizes the presence of circulating antibodies (IgG, for example) to H. pylori. Serology has a high sensitivity and specificity for identification of H. pylori. A positive test does not correlate with the presence or absence of a peptic ulcer. A negative test is very useful clinically because H. pylori is not present and therefore can not be the source of that patient's symptoms. Serologic antibodies will remain positive, potentially indefinitely, despite successful eradication of H. pylori. Serology should not be relied on to assess for

eradication after antibiotic therapy, nor should it be concluded that there is re-infection if serology is checked in the future. Breath testing involves oral administration of radiolabeled (C^{13} or C^{14}) urea. If H. pylori is present, bacterial urease will generate radiolabeled carbon dioxide, which will pass into the bloodstream and be exhaled from the lungs. Urea breath testing can be used to non-invasively assess for successful eradication of H. pylori.

Invasive tests for detection of H. pylori include rapid urease tests (RUTS) and histologic examination; both require endoscopy with mucosal biopsy. RUTS involve placing a biopsy specimen into urea medium. If bacteria are present in the biopsy specimen, the urea will be converted to ammonia resulting in a color change in the medium due to alteration in pH. RUTS have good sensitivity and specificity, results are rapidly available, and there is little additional cost beyond that of endoscopy. Histologic assessment of endoscopic biopsy specimens has been considered the gold standard, especially to document the successful eradication after antibiotic therapy. Bacteria can be identified on routine H&E stain or by special stains. Histology not only allows for the detection of bacteria but also the identification of the degree of gastritis, including intestinal metaplasia.

Unlike most infectious diseases, bacterial culture for H. pylori has limited clinical usefulness. Culture is the least sensitive of the diagnostic tests. Special culture media and highly experienced technicians are required. In the rare patient with persistent H. pylori infection despite attempted eradication therapy, culture with antibiotic sensitivity

analysis can be useful to identify antibiotic resistant strains. Antibiotic resistance is uncommon in the U.S., although those people previously exposed to metronidazole are more likely to develop metronidazole-resistant H. pylori. Antibiotic monotherapy is associated with poor eradication rates; multi-drug combination regimens are required to achieve high rates of eradication. This is due in part to the organism residing under the mucus gel layer, the rapid removal of antibiotics from the stomach, and the importance of antibiotic tissue concentrations rather that serum concentrations.

Autoimmune Atrophic Gastritis. Autoimmune atrophic gastritis, also known as type A gastritis or pernicious anemia, is characterized by chronic gastritis, atrophy of the oxyntic glands, and hypo- or achlorhydria. The pattern of inheritance is autosomal dominant. Autoantibody formation to the parietal cell and intrinsic factor are found in the majority of patients with pernicious anemia. Damage is confined to the body and fundus of the stomach; the locations of the oxyntic glands. The anti-parietal antibody appears to be directed against the H^+, K^+ - ATPase enzyme. The atrophic gastric glands have a higher predisposition for undergoing intestinal metaplasia. In Scandinavian countries, higher rates of progression to dysplasia and gastric adenocarcinoma have been reported. The profound hypoacidity leads to unopposed gastrin release from antral G-cells. The resultant hypergastrinemia leads to marked hyperplasia of the ECL cells. ECL cell hyperplasia has been associated with an increased risk of gastric carcinoid formation.

Duodenal Mucosa

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The duodenum is the first portion of the small intestine with a length of 20- to 25-cm ending at the ligament of Treitz. The duodenum resides posteriorly in the abdominal cavity and is in close proximity to the pancreas. The duodenal mucosa has a granular texture due to the presence of villi projecting above the mucosal surface. Villi are finger-like projections which serve to increase the intestinal surface area thus maximizing the absorptive and digestive functions. Villi are lined primarily by tall columnar absortive enterocytes which have a lush brush border of microvilli. Interspersed among the enterocytes are mucus-secreting goblet cells. The ratio of villus height to intestinal crypt depth in adults is between 3:1 and 5:1. The base of the crypts is the site of cell mitoses important in surface restitution and repair. Paneth cells are also found in the crypts. Mucus-secreting glands, called Brunner's glands, are found in the duodenal submucosa.

Cholecystokinin (CCK) is a polypeptide hormone found in endocrine cells (I cells) of the duodenum and proximal jejunum. Release of CCK is stimulated by the presence of nutrients, especially amino acids, entering the duodenum. The principal physiologic actions of CCK are stimulation of pancreatic enzyme secretion and contraction of the gallbladder. CCK also inhibits gastrin release and therefore gastric acid secretion. CCK participates in the regulation of gastric emptying and intestinal motility.

Secretin is a 27 amino acid hormone found in endocrine cells (S cells) of the duodenum and small intestine. Release of secretin is stimulated upon acid entering the duodenum. The principal physiologic action of secretin is stimulation of pancreatic

bicarbonate and water secretion. Secretin also inhibits gastrin release, acid secretion, and gastric emptying.

Duodenitis

Inflammation of the duodenal mucosa is typically caused by similar processes as seen with inflammation of the gastric mucosa. Duodenitis has been divided into three grades: grade 1 reveals an increase in the mononuclear cell population of the lamina propria; grade 2 reveals neutrophils in the lamina propria and epithelium; grade 3 has associated inflammation and surface erosion or ulceration. Hyperplasia of the submucosal Brunner's glands may give the proximal duodenum a nodular appearance. In gastric acid hypersecretion, gastric metaplasia of the duodenal epithelium is often noted on histologic biopsy. The patches of metaplastic epithelium may be infected by H. pylori, which is the postulated mechanism for H. pylori-induced duodenal ulcer disease.

Peptic Ulcer Disease

Peptic ulcer disease (PUD) is a major health problem in the U.S. with an estimated 400-500,000 new cases/year. Direct health care costs exceed 2 billion dollars/year, which does not include time lost from work, reduced productivity, and other indirect costs. In the U.S. there are approximately 4 million ulcer recurrences/year. Millions more are taking over-the-counter or prescription medication to alleviate ulcer type symptoms.

Historically, gastric acid was thought to be the only factor responsible for ulcer formation. "No acid, no ulcer" was a common statement. Initial acid secretory studies suggested patients with duodenal ulcers were hypersecretors of acid, especially ay night. However, subsequent studies have shown less than 30% of DUs are in patients with acid hypersecretion. Peptic ulcer disease is now considered primarily an infectious disease since the discovery of the association between PUD and H. pylori infection. Over 90% of duodenal ulcers and 70-80% of gastric ulcers are associated with H. pylori infection. Successful eradication of H. pylori has been shown to dramatically reduce the rates of ulcer recurrence from 70% to 2% within one year. Peptic ulcer disease should be thought of as an imbalance between host protective factors and aggressive factors. Protective factors include mucus production, bicarbonate secretion, blood flow, cell restitution and repair, prostaglandins, and normal gastroduodenal motility. Aggressive factors include acid, pepsin, bacteria, bile acids, pancreatic enzymes, drugs (ASA, NSAIDs, steroids), gastric emptying disorders, heredity, and cigarettes. Several chronic medical disorders have been associated with an increased incidence of PUD, including chronic renal failure, chronic obstructive pulmonary disease, and cirrhosis.

The most common symptoms of PUD is burning epigastric pain. Pain occurring 1 to 3 hours after a meal, improving with food, and awakening the patient from sleep are more typical for duodenal rather than gastric ulcer. Dyspeptic symptoms, including nausea, vomiting, gas, bloating, and belching, are seen with PUD but are poorly predictive of the presence or absence of disease. In fact, the signs and symptoms

associated with PUD are neither sensitive nor specific and therefore are not predictive of the presence or absence of disease. The physical examination is usually unremarkable in those with uncomplicated PUD. Complications of PUD include hemorrhage, obstruction, and perforation thus patients may present with hematemesis, melena, gastric outlet obstruction, or an acute abdomen. Laboratory evaluation in uncomplicated PUD is typically normal, although H. pylori serology and, on occasion, a fasting gastrin level may be helpful.

PUD is typically diagnosed by either an upper gastrointestinal (UGI) barium x-ray series or by upper endoscopy. An UGI series is non-invasive and less expensive than endoscopy. However, it can overlook 10-20% of ulcers, especially small ulcers in the duodenal bulb where it is difficult distinguishing between an old ulcer scar versus a small active ulcer. Upper endoscopy allows for direct visualization of the UGI tract mucosa with the ability to obtain biopsies for histology.

Treatment of PUD has changed dramatically over the past several decades. Surgical interventions, including antrectomy, pyloroplasty, and vagotomy, were once the standard of care of PUD. Now-a-days, surgery is only necessary for those cases of non-healing ulcers or for complications of PUD. Medical therapy heals the vast majority of ulcers. Goals of medical therapy should include the rapid and safe resolution of pain, induction of ulcer healing, prevention of ulcer complications, and the prevention of ulcer recurrence. Lifestyle behavioral modifications should be encouraged, including the cessation of cigarette smoking, elimination of NSAID use, and reduction of alcohol

consumption. Specific dietary restrictions have no proven clinical benefits in the management of PUD.

Antacids. Antacids were the first medical treatment to show improved ulcer healing rates as compared to placebo. They work by rapid neutralization of luminal acid. Unfortunately, they have a brief duration of action, thus requiring frequent dose administration for ulcer healing. They are safe, inexpensive, and available over-the-counter. Common side effects include constipation (aluminum antacids), diarrhea (magnesium antacids), sodium load and possible alkalosis (sodium bicarbonate), or elevation of serum calcium (calcium antacids). Antacids may decrease the absorption of other medications when taken at similar times.

H_2 Antagonists. The first H_2 blocker developed was cimetidine (Tagamet) in the 1970's; there are currently several others commercially available by prescription or over-the-counter. H_2 blockers decrease basal and stimulated acid secretion by binding to the histamine receptor on the parietal cell. H_2 blockers are an extremely safe class of drugs, although they can cross the blood-brain barrier, placenta, and are excreted into breast milk. H_2 blockers also bind to and inhibit cytochrome P450 in the liver, which can interfere with the metabolism of drugs, including coumadin, theophylline, dilantin, and lidocaine. The different H_2 blockers are equally efficacious at healing ulcers.

H^+, K^+-ATPase Inhibitors. The proton pump inhibitors are the most potent drugs available to suppress gastric acid secretion. They are substituted benzimidazoles that covalently and irreversibly bind to the cystine residues of the H^+, K^+-ATPase pump.

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Proton pump inhibitors are prodrugs with a pKa of 4 packaged for timed release and absorption from the small intestine. They then become concentrated in the secretory canaliculus of the parietal cell. The local pH in the secretory canaliculus is less than 1.5 which activates the prodrug via protonation to form a sulfenamide. The activated form then irreversibly binds to the H$^+$, K$^+$ -ATPase pump. Acid secretion from the inhibited pumps is completely blocked until new pumps are synthesized, which requires approximately 24 hours. The duration of action is therefore approximately 24 hours even though the serum half life is only 8 hours. The profound hypochlorhydria has been associated with significant hypergastrinemia, which initially raised concerns about the potential risk for ECL cell hyperplasia and inducement of gastric carcinoids in long-term use. However, recent data suggest this risk is minimal and of little clinical significance in humans.

Prostaglandins. The prostaglandin E$_1$ analog, misoprostol (Cytotec), decreases acid secretion by binding to its receptor on the basolateral membrane of the parietal cell, which leads to decreased cyclic AMP levels. Prostaglandins also exert a mucosal protective effect by stimulating mucus and bicarbonate secretion, enhancing mucosal blood flow, and promoting mucosal cell restitution and repair. Prostaglandins have been used to heal peptic ulcers and to prevent NSAID-induced gastric and duodenal ulcers.

Anticholinergics. Anticholinergic agents block the muscarinic (M$_3$) cholinergic receptor on the parietal cell. They weakly inhibit both basal and stimulated acid secretion. Anticholinergic agents have limited clinical usefulness in acid suppression

therapy due to their numerous unacceptable side effects, including increased heart rate, dilated pupils, dry mouth, urinary retention, and ileus.

Sucralfate. Sucralfate (Carafate) is a basic salt composed of sucrose, aluminum, and octasulfate. It has no effect on acid secretion but, instead, is presumed to have a mucosal protective effect. In the presence of acid, it dissociates into aluminum hydroxide and sucrose sulfate. The sucrose moiety polymerizes into a thick paste, which readily adheres to any denuded or ulcerated mucosa. Sucralfate is useful in the treatment of PUD and in the prevention of stress related ulcers. It can adsorb bile salts, thus may have a role in the treatment of bile reflux. Side effects of sucralfate include adsorption of other drugs, constipation, and bezoar formation.

Antibiotics. The successful management of peptic ulcer disease requires the successful eradication of H. pylori. Eradication is associated with a dramatic reduction in the incidence of ulcer recurrence. Commonly used regimens and indications for H. pylori eradication are shown in Tables 11 and 12 respectively.

Zollinger-Ellison Syndrome

Zollinger-Ellison Syndrome (ZES) is due to hypersecretion of gastrin from a non-beta islet cell tumor (gastrinoma). The hypergastrinemia results in marked hypersecretion of acid and severe peptic ulcer disease. The symptoms and appearance of ulcers in ZES are often indistinguishable from routine peptic ulcer disease. ZES should be suspected in patients with ulcers beyond the first portion of the duodenum, presence of multiple ulcers, ulcers refractory to standard therapy, or ulcers complicated by hemorrhage, perforation, or

obstruction. Diarrhea is a common clinical manifestation of ZES due to the tremendous amount of acid entering the small intestine resulting in villous atrophy. The hyperacidity also results in pancreatic enzyme inactivation with steatorrhea. Approximately 25% of patients with ZES have multiple endocrine neoplasia type 1 (MEN 1) syndrome. This autosomal dominant genetic disorder is associated with primary tumors in the pituitary, parathyroid, and pancreas. ZES is diagnosed if the serum gastrin levels is greater than 1000 pg/ml in the setting of acid secretion. The secretin test is helpful in those patients with gastrin levels below 1000 pg/ml. In normal patients, intravenous secretin causes a drop in serum gastrin levels; however, in ZES patients there is a paradoxical increase noted. High-dose acid inhibition therapy and surgical resection of the gastrinoma, if localizable, are the mainstays of ZES treatment.

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