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Acid Suppression: Optimizing Therapy for Gastroduodenal Ulcer Healing, Gastroesophageal Reflux Disease, and Stress-Related Erosive Syndrome

M. MICHAEL WOLFE* and GEORGE SACHS†

*Section of Gastroenterology, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts; and †Division of Gastroenterology, UCLA School of Medicine and West Los Angeles VA Medical Center, Los Angeles, California

One of the hallmarks of the mammalian stomach is its ability to secrete large quantities of concentrated (0.16 mol/L) hydrochloric acid (HCl).[1] Although it is generally assumed that gastric acid and the proteolytic enzyme pepsin are required to initiate digestion, achlorhydric individuals generally do not develop malabsorption unless small bowel bacterial overgrowth is present. It is thus likely that the ability of the stomach to secrete acid evolved primarily from a need to sustain a sterile intragastric milieu. Organisms that possessed the capacity to kill ingested bacteria and other microbes were able to avoid the development of enteric colonization, and thereby ensure both efficient absorption of nutrients and prevention of systemic infections.[1] Nevertheless, when present, gastric acid does play a significant role in protein hydrolysis and other aspects of the digestive process, and under various conditions, acid may play an etiologic role in producing various forms of discomfort and inciting esophageal and gastroduodenal mucosal injury.

The normal human stomach contains approximately 1 billion parietal cells that secrete hydrogen ions into the gastric lumen in response to various physiological stimuli. The generation of H^+ ions is mediated by 3 pathways: neurocrine, paracrine, and endocrine (Figure 1). The principal neurocrine transmitter is acetylcholine, which is released by vagal postganglionic neurons and appears to stimulate H^+ ion generation directly via a parietal cell muscarinic M_3 receptor. Histamine is the primary paracrine transmitter that binds to H_2-specific receptors on parietal cells. Adenylate cyclase is then activated, leading to an increase in adenosine 3′,5′-cyclic monophosphate (cAMP) levels and subsequent generation of H^+ ions. The secretion of gastrin from antral G cells comprises the endocrine pathway and stimulates H^+ ion generation both directly and indirectly, the latter by stimulating histamine secretion from enterochromaffin-like (ECL) cells of the corpus and fundus. Interactions among neurocrine, paracrine, and endocrine pathways are coordinated, and histamine appears to represent the dominant route, because gastrin stimulates acid secretion principally by promoting histamine release from ECL cells.[2,3] Thus, ECL cells are often referred to as "controller" cells in the process of gastric acid secretion.

A negative feedback loop governs both gastrin release and the return of acid secretion to basal level.[1,4–6] This autoregulatory mechanism prevents postprandial acid hypersecretion. After ingestion of a meal, gastrin release stimulates secretion of gastric acid. The intraluminal pH begins to decrease, which stimulates release of somatostatin from antral D cells, possibly through the activation of calcitonin gene–related peptide (CGRP) neurons.[5,7] Somatostatin then appears to act via a paracrine mechanism to inhibit further release of gastrin from G cells.[8] Somatostatin produced by D cells in the gastric corpus and fundus may also directly inhibit acid secretion from parietal cells and may suppress histamine release from ECL cells (Figure 1).[6,9] Other recent observations indicate that several other neurotransmitters, including vasoactive intestinal peptide (VIP), galanin, and pituitary adenylate cyclase–activating peptide, may play important roles in regulating gastric acid secretion, both directly and indirectly, under physiological conditions.[10]

Pathophysiology of Acid-Related Disorders

Gastroduodenal (Peptic) Ulcer

The treatment of duodenal ulcer (DU) has served as the basis (correctly or incorrectly) for the management of nearly all acid-related disorders. This supposition in all likelihood contributed to delays in the optimal management of other gastrointestinal (GI) disorders in which

Abbreviations used in this paper: DU, duodenal ulcer; ECL, enterochromaffin-like; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GU, gastric ulcer; NCCP, noncardiac chest pain; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

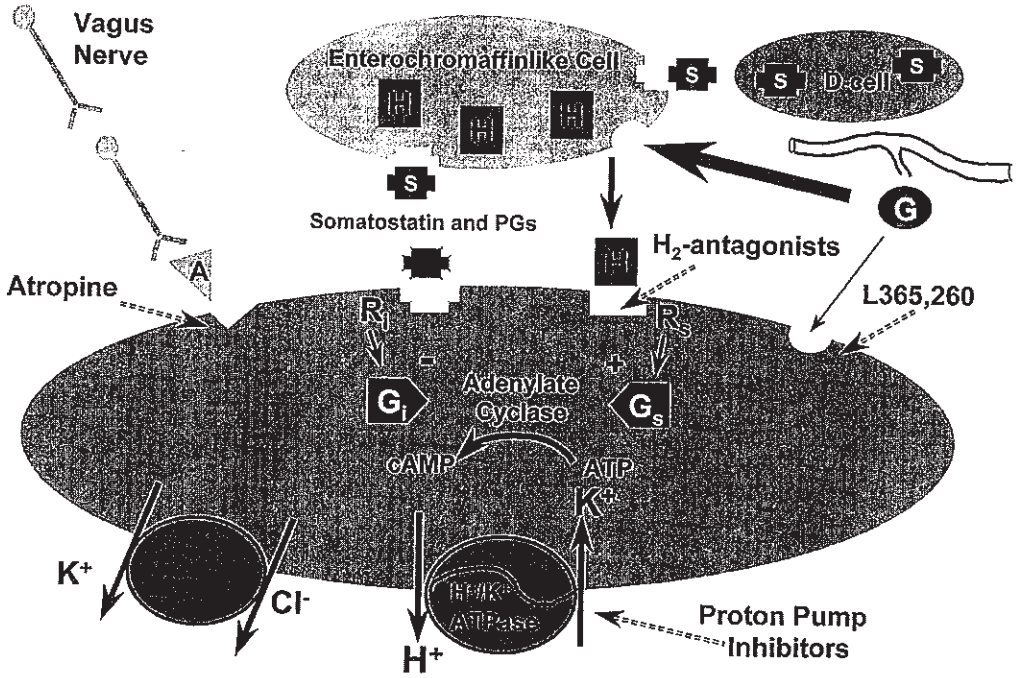

Figure 1. Schematic representation of the factors influencing gastric acid secretion by the parietal cell, depicting neurocrine (acetylcholine and other neurotransmitters from vagal efferent neurons), paracrine (somatostatin from D cells and histamine from gastric ECL cells), and endocrine (circulating gastrin) factors. *Dashed arrows* indicate potential sites of pharmacological inhibition of acid secretion, either via receptor antagonism or via inhibition of H^+,K^+-ATPase. A, acetylcholine and other neurotransmitters; H, histamine; G, gastrin; L365,260, synthetic gastrin receptor antagonist; PG, prostaglandin; S, somatostatin.

acid plays an etiologic role in producing symptoms and causing mucosal injury, such as gastroesophageal reflux disease (GERD). Although patients with gastric ulcers (GUs) tend to have normal or reduced levels of acid secretion,[1] the average DU patient is an acid hypersecretor. When compared with age-matched controls, DU patients secrete ~70% more acid during the day (meal-stimulated) and about 150% more acid at night (basal secretion) (Figure 2).[11] Postprandial gastric acid secretion is regulated primarily by increases in gastrin expression, which is controlled by a negative feedback loop. Individuals infected with *Helicobacter pylori* have been shown to have a diminished number of somatostatin-secreting D cells, which decreases the magnitude of the response to luminal acidification.[12–14] Thus, in patients with *H. pylori* infection limited to the antrum, the negative feedback inhibition of gastrin release is attenuated, resulting in higher postprandial gastrin levels and hypersecretion of acid.

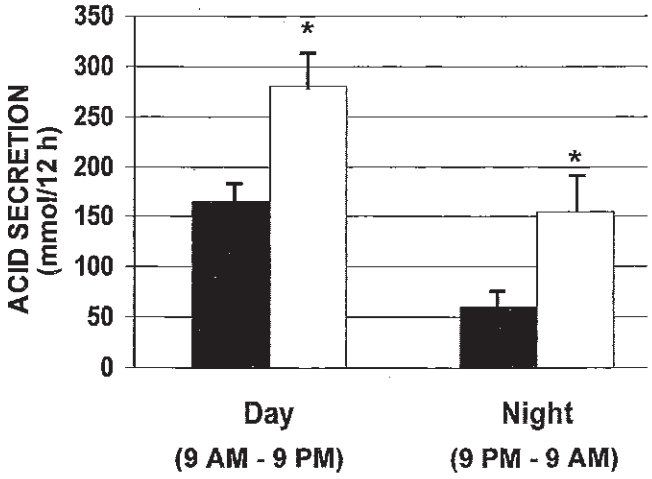

Figure 2. Gastric acid secretion during the day and night in patients with DU (n = 8) and in age-matched controls (n = 7). Acid secretion is expressed as the mean + SE in millimoles per 12 hours. *$P < 0.05$

Despite the existence of meal-induced hyperchlorhydria in DU patients, the presence of food in the stomach has a buffering effect that may protect the gastroduodenal mucosa from acid-induced injury. However, at night and during other prolonged periods of fasting, acid bathes the "bare" mucosa, and in DU patients, the increase in nocturnal acid secretion magnifies this effect. Duodenal bicarbonate secretion also appears to be impaired in patients with DU,[15] as well as in those infected with *H. pylori*, making the mucosal exposure to acid even greater. These observations, as discussed below, form the rationale for single nocturnal dosing of H_2-receptor antagonists in the treatment of DU, a mode of therapy that is at least as effective as multiple dosing regimens.

Clearly, factors other than acid and pepsin are involved in the pathogenesis of peptic ulcer disease (PUD), because only 30% of patients with DUs and very few patients with GUs are hyperchlorhydric.[1] The balance between aggressive factors that act to injure the gastroduodenal mucosa and defensive factors that normally protect against corrosive agents is also important. When this delicate balance is disrupted for any reason, mucosal injury may ensue.[1] These defensive properties appear to be mediated to a large extent by endogenous prostaglan-

synthesis of any or all are diminished, the ability of the gastroduodenal mucosa to resist injury is decreased. Thus, even normal rates of acid secretion may be sufficient to injure the mucosa and produce gastroduodenal ulcers. Nevertheless, even in DU patients who are normal secretors of acid, a reduction in the rate of acid secretion is the most efficient means of healing ulcers.[1]

Although a large number of gastroduodenal ulcers are associated with *H. pylori* infection, at least 60% of individuals with complicated ulcers (e.g., hemorrhage or perforation) report the use of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin.[16] Mucosal injury associated with NSAID use is initiated topically by the acidic nature of NSAIDs.[17] Topical mucosal injury may also occur as a result of indirect mechanisms, mediated through the biliary excretion and subsequent duodenogastric reflux of active NSAID metabolites.[18,19] Topical injury caused by NSAIDs certainly contributes significantly to the development of gastroduodenal mucosal injury, but the systemic effects of these agents appear to play the predominant role,[17,20,21] largely through the decreased synthesis of mucosal prostaglandins.[22] Avoidance of topical mucosal injury by enteric-coated aspirin preparations[22] or by the parenteral[23] or rectal[24] administration of NSAIDs does not prevent the development of ulcer complications. Moreover, doses of aspirin as low as 10 mg are sufficient to significantly suppress gastric mucosal prostaglandin synthesis.[25] A decrease in the above protective mechanisms normally stimulated by prostaglandins enables endogenous gastric acid to incite mucosal injury.

In recent years, it has become evident that the actual percentage of ulcers associated with *H. pylori* may not be 90%–95% as often reported, but may be as low as 32% in non–referral-based populations.[26] Furthermore, despite the inclination to ascribe the etiology of ulcers in such individuals to NSAIDs, the use of these agents clearly does not account for the balance of the cases. Finally, the vast majority of remaining individuals do not have the Zollinger–Ellison syndrome (ZES) or another unusual cause of gastroduodenal ulcer. Thus, while peptic ulceration involves the participation of several factors, as first stated by Karl Schwarz[27] in 1910: "*Ohne sauren Magensaft, kein peptisches Geschwür*," i.e., "No acid, no ulcer." The erosive properties of acid continue to play a central role in the pathogenesis of gastroduodenal mucosal ulceration, and conversely, acid suppression therapy remains the cornerstone of therapy.

GERD

Although the principal aggressive factor involved of GERD is the presence of acid in the esophagus, the disorder does not usually result from the hypersecretion of gastric acid.[28] Rather, GERD occurs as a result of several abnormalities in motor function of the lower esophagus and the lower esophageal sphincter (LES). Despite the etiologic role played by these important motor abnormalities, the severity of symptoms, most notably heartburn, and esophageal mucosal injury can be correlated with the total time that the esophageal mucosa is exposed to acid. Gastric acid thus also constitutes a critical element in the pathogenesis of GERD, and acid suppression comprises the principal mechanism for therapy. However, the optimal timing and degree of acid suppression differ significantly in GERD patients compared with the treatment of gastroduodenal ulcer (see below).

Stress-Related Erosive Syndrome

Many terms have been used to describe this entity, including stress ulcer syndrome, stress gastritis, stress-related mucosal disease, and stress-related erosive syndrome (SRES).[29,30] The principal feature of SRES is its relationship to serious systemic disease, such as sepsis, massive burn injury, head injury associated with increased intracranial pressure, severe trauma, and multiple-system organ failure. A meta-analysis of 2252 patients by Cook et al.[31] identified mechanical ventilation and coagulopathy as the 2 singlemost important risk factors. Although the pathophysiology is multifactorial and definitely includes a component of ischemia, which compromises gastric mucosal integrity, luminal acid plays a dominant role in producing the multiple erosive lesions characteristic of the entity. Fiddian-Green et al.[32] emphasized the importance of H^+ ion back-diffusion by demonstrating a high correlation between the degree of intramural pH and the development of SRES. Furthermore, most, but not all, methods for preventing massive hemorrhage-associated SRES include the alkalinization of gastric contents.[33]

Pharmacology of Parietal Cell Receptors

The parietal cell possesses a unique morphology that differs markedly between the resting and stimulated states.[1] Mitochondria occupy 34% of its cell volume, indicative of the importance of adenosine triphosphate (ATP) synthesis as an energy source required for the active transport of H^+ ions out of the cell against a 3,000,000:1 ionic gradient. A large percentage of resting cell volume is also occupied by tubulovesicles, which are elongated

secretory canaliculus, a small invaginated area of the apical membrane. Upon stimulation, which is generally accomplished by eating a meal, the tubulovesicles decrease in number and become transformed into microvilli around the secretory canaliculus, which serves to greatly expand the surface area of the parietal cell in preparation for the secretion of large quantities of HCl. The parietal cell also possesses several different receptors for stimulatory and inhibitory ligands on its basolateral membrane (Figure 1).

Histamine H_2 Receptor and Its Antagonists

The histamine receptor belongs to a large family of G protein–linked receptors possessing 7 transmembrane domains.[34] Despite the recognition that histamine stimulates gastric acid secretion, it was not until 1966, when Ash and Schield[35] described H_1 and H_2 receptors for histamine, that the possibility of inhibiting acid secretion with histamine antagonists was proposed. In 1970, Black et al.[36] described selective histamine H_2-receptor inhibition and initiated the search for pharmacological agents that could effectively suppress the secretion of acid. Within 10 years of the release of cimetidine in the United States in 1977, 3 additional H_2-receptor antagonists—ranitidine, famotidine, and nizatidine—became available for use throughout the world. All 4 drugs (Figure 3) suppress basal and meal-stimulated acid secretion, albeit to a lesser degree than proton pump inhibitors (PPIs) discussed below. Despite similar therapeutic profiles, some differences do exist with regard to the agents' pharmacokinetic properties (Table 1), most of which are clinically insignificant.[37] The elimination of these drugs occurs by a combination of hepatic metabolism and urinary excretion, and although hepatic dysfunction does not alter their pharmacokinetic properties, dose reductions are recommended for all individuals with varying degrees of renal impairment (Table 2).[37] H_2-receptor antagonists as a class possess an unsurpassed

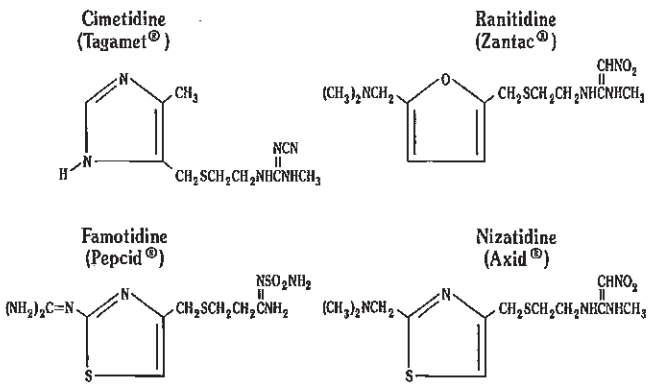

Table 1. Comparison of the Histamine H_2-Receptor Antagonists

	Cimetidine	Ranitidine	Famotidine	Nizatidine
Bioavailability (%)	80	50	40	70
Relative potency	1	5–10	32	5–10
Circulatory $t_{1/2}$ (*h*)	1.5–2.3	1.6–2.4	2.5–4	1.1–1.6
Biological $t_{1/2}$[a] (*h*)	6	8	12	8
Relative effect on cytochrome P450 metabolism	1	0.1	0	0

$t_{1/2}$, half-life.
[a]Approximate values.
Adapted and reprinted with permission.[37]

safety record, and in 1995 became available for use in the United States without prescription.

Muscarinic Receptor and Its Antagonists

The central nervous system, particularly via the vagus nerve, plays a dominant role in regulating basal acid secretion, as well as the cephalic phase of meal-stimulated acid secretion. Extracts of belladonna were used to treat dyspepsia since the time of the Roman empire, and in the recent past, nonspecific antimuscarinic agents such as atropine and propantheline bromide were used as inhibitors of gastric acid secretion. These drugs were associated with many adverse effects, including drowsiness, dry mouth, blurry vision, and urinary retention, and as a result are rarely used today. To date, however, 5 muscarinic receptors have been subtyped and cloned, and although all are G protein coupled, they signal different intracellular pathways. In vitro characterization of gastric acid secretion has indicated that the parietal cell normally expresses the M_3 subtype.[38] Clinically, the M_1 antagonists, pirenzepine and telenzepine, are effective inhibitors of acid secretion and probably

Table 2. Histamine H_2-Receptor Antagonist Dosing Adjustments With Renal Insufficiency

Drug	Creatinine clearance (*mL/min*)	Dose (*mg/day*)[a]
Cimetidine	>30	800
	15–30	600
	<15	400
Ranitidine	>75	300
	30–75	225
	15–30	150
	<15	75
Famotidine	>75	40
	30–75	30
	15–30	20
	<15	10
Nizatidine	>75	300
	30–75	225
	15–30	150
	<15	75

[a]Dosing for gastroduodenal ulcer.

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