YALE JOURNAL OF BIOLOGY AND MEDICINE 72 (1999), pp. 173-180.

Pharmacologic Modulation of Motility

Richard W. McCallum[a]

Department of Gastroenterology and Hepatology, Center for GI Motility Disorders, University of Kansas Medical Center, Kansas City, Kansas

Etiologically, gastroesophageal reflux disease (GERD) can be regarded as motility disorder. Although blocking acid is effective in the treatment of GERD, it does not overcome the underlying pathologic factors that allow acid, pepcin, and bile to reflux into the esophagus. Prokinetic agents address the upper gastrointestinal motility disturbances contributing to GERD and, thus, have an important role in the short- and long-term medical management of reflux esophagitis. This paper discusses the rationale for the effectiveness of pharmacologic modulation by reviewing current concepts and postulated theories about the mechanisms underlying the neuromuscular abnormalities. The multifactorial aspects of GERD are addressed and the potential for tailoring medical therapy also emphasized.

ESOPHAGEAL MOTOR ACTIVITY IN REFLUX ESOPHAGITIS

Because acid is the major noxious agent in the refluxate material, the severity of esophagitis depends on the duration of time the esophagus is exposed to acid material. The esophageal acid exposure time or acid reflux time is a function of the frequency of reflux episodes, as well as the duration of each reflux episode. The frequency of reflux episodes is determined by the factors that impair the antireflux barrier. On the other hand, the ability to clear individual acid reflux episode and acid clearance time is determined by peristaltic activity of the esophagus and salivary neutralization capacity.

Helm et al. have contributed significantly to our understanding of the various factors that are important in the acid clearance times. The methodology uses the introduction of a small bolus of acid into the esophagus (usually 15 ml) and then asking the individual to swallow at 30 sec intervals. With the introduction of hydrochloric acid into the esophagus, the esophageal pH usually decreases to 1.2, and acid clearance time is usually counted as the time for the esophageal pH to recover to 4. The bolus or volume clearance can also be measured with the acid clearance by labeling the acid with radioactive material (usually technetium) and monitoring the radioactivity in the esophagus and esophageal pH simultaneously.

[a]To whom all correspondence should be addressed: Richard W. McCallum, M.D., F.A.C., F.A.C.G., Professor of Medicine, Chief of Gastroenterology and Hepatology, Director of Center for GI Motility Disorders, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160. Tel.: 913-588-6003; Fax: 913-588-3975. E-mail: rmccalu@kumc.edu.

[b]Abbreviations: EMG, electromyogram; GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; GEJ, gastroesophageal junction; LES, lower esophageal sphincter; MMC, migrating motor complex; TLESR, transient lower esophageal sphincter relax-

Normally, one or two peristaltic contractions clears most of the bolus from the esophagus into the stomach without changing the esophageal pH. This initial clearance of bolus is termed the volume clearance. Once the majority of the volume of acid is cleared from the esophagus, usually a small amount of acid sticks to the surface of the mucosa of the esophagus and the pH probe. This is cleared with subsequent swallows (acid neutralization). It is the saliva accompanying swallows that neutralizes acid and restores the esophageal pH to normal. Replacing saliva with water markedly prolongs acid clearance. These observations suggest that there are substances in the saliva that can neutralize acid in the esophagus. Fifty percent of the buffering capacity of saliva can be attributed to the salivary proteins. Reduction of salivary flow by atropine markedly prolongs acid clearance time, and agents such as bethanechol and oral lozenges that stimulate salivary flow and bicarbonate production markedly accelerates acid clearance times. Acid clearance time is markedly prolonged during sleep when salivation ceases.

Volume clearance and acid neutralization are both important in the clearance of acid from the esophagus. The importance of volume clearance can be recognized by the fact that a 15 ml bolus of acid would require 105 ml of saliva for its neutralization in the absence of a volume clearance mechanism. With the rate of basal salivary flow, which is approximately 1 ml per minute, it would take 1 hr and 45 min for its neutralization. However, with bolus clearance, 10 to 15 swallows at 30 sec intervals return the esophageal pH to normal.

Is salivary flow impaired in patients wit reflux esophagitis? A study by Sonnenberg et al. showed that there was no difference in the resting salivary function among normal subjects and patients with reflux disease. However, salivary flow is reduced with age. Smoking diminishes the salivary flow and its bicarbonate concentration, perhaps partially explaining the deleterious effect of cigarette smoking on the esophagus. Salivary flow increases in response to acid instillation into the esophagus or to heartburn. This esophagosalivary reflex is again a function of age, and it appears that as one gets older this reflex increase in salivary flow rate decreases. Helm et al. have suggested that this esophagosalivary reflex is absent in patients with severe esophagitis and, hence, may play an important role in the pathogenesis of reflux disease.

ROLE OF HIATUS HERNIA IN REFLUX ESOPHAGITIS

Is hiatus hernia important in reflux disease? It is ironic that apparently such a simple question has dodged us for so long. In the 1950s and 1960s, hiatus hernia was synonymous with reflux disease. In the 1970s and 1980s, it was not felt to be of primary importance, but interest in its pathophysiological role has reappeared in the 1990s. The major deterrent to its importance lies in its common presence in asymptomatic subjects, and the observation that 5 percent to 20 percent of patients with gastroesophageal reflux (GER)[b] do not have hiatal hernias. However, one cannot ignore the facts that more than 95 percent of patients with significant GER disease (GERD) have hiatal hernias, and that all successful antireflux operations include reduction of hiatal hernia. The Allison operation, which only reduces hernias, is successful in a significant number of patients, and recurrence of the hernia is a common finding in patients with a return of symptoms following antireflux surgery. All of these arguments should refocus our attention and research on the pathophysiological significance of hernias in GERD.

Recent studies have focused on the effect of a hernia on acid clearance. Using simultaneous esophageal pH monitoring and scintiscanning, we found that normally a bolus of radiolabeled acid is cleared

from the esophagus soon after its injection either by primary (caused by the first swallow) or secondary peristalsis. However, patients with a hiatal hernia retain a portion of the injected bolus in the hernial sac. This retained bolus re-refluxes with subsequent swallow-induced LES relaxations. Thus, delayed disappearance of acid in patients with a hiatal hernia is not delayed clearance but is new reflux from the hernia.

Delayed acid clearance in patients with reflux esophagitis and hiatal hernias has been recognized by a number of investigators. Booth et al. found this to be the case and so did DeMeester et al. Stanciu and Bennett found no correlation of hiatus hernia with acid clearance times. However, Johnson reported accelerated acid clearance after an antireflux operation in patients with reflux esophagitis. Sloan and Kahrilas have recently identified that the reason for the heterogeneity in acid clearance times with hiatus hernia is related to the type of hiatal hernia: reducible or non-reducible. It is only the non-reducible hernias that trap the bolus and demonstrate re-reflux phenomena with the swallows that are associated with delayed acid clearance time. The reducible hernia, on the other hand, does not impair the acid clearance mechanism.

Better understanding of the role of crural diaphragm at the esophagogastric junction will most likely clarify the pathophysiological significance of hiatal hernias in GERD. It is more than likely that the hernia contributes to the pathophysiology of reflux disease by other mechanisms, in addition to impaired acid clearance. McCallum and Mittal, as well as Holloway and Dent, have observed inspiration-related reflux, which seems to occur exclusively in patients with hiatal hernias and severe reflux disease. One mechanism by which inspiration may induce GER could be related to contraction of the crural diaphragm. This contraction may lead to compartmentalization of a part of the stomach above the diaphragm, facilitating reflux of the contents from a herniated stomach into the esophagus. Despite the current enthusiasm, I believe that careful and prospective studies need to be performed before one may accept the true role of the hernia in reflux disease.

The major limiting factor in hiatal hernia research is the lack of perfect methodology to identify and thus define hiatal hernia. Most studies use barium swallow and provocative maneuvers, such as abdominal compression, to detect hernias. The maneuvers are often unphysiological and do not distinguish between reducible and non-reducible hernias. Endoscopic diagnosis is subjective, and it also does not address the issue of reducibility. Manometry may be more physiological than these other methods, particularly a simultaneous pressure and crural diaphragmatic electromyogram (EMG) recording technique. This technique can precisely determine the location of the LES, the crural diaphragm, and their relationship to each other in a normal subject. A similar technique could be used to detect hiatal hernias more precisely in order to address the importance of hiatal hernia in reflux disease.

WHAT IS THE EFFECT OF CHOLINERGIC STIMULATION ON ESOPHAGEAL MOTILITY AND CLEARANCE IN GERD?

The pharmacological basis of esophageal peristalsis has been elucidated. Esophageal peristalsis is the major mechanism responsible for the clearance of both the swallowed food bolus and the refluxed gastric content. Primary swallowing-induced peristalsis empties the food bolus, while secondary peristalsis (induced by the presence of gastric acid) clears refluxed material, particularly at night. A minimum contraction amplitude of 30 mmHg is required for clearance, which is incomplete at lower contraction amplitudes and when peristaltic progression of the contraction fails.

Cholinergic stimulation is excitatory to esophageal peristalsis while nitrergic innervation is inhibitory. Experimental studies in cats, monkeys and humans demonstrate that atropine blockade reduces the amplitude of esophageal contractions and inhibits the progression of the peristaltic wave from the striated muscle to the smooth muscle. Atropine blockade has no effect on the propagation velocity in the smooth muscle itself. The inhibitory role of nitric oxide can be blocked by $_{L}$-nitro-arginine-methyl-ester and nitric oxide scavengers, such as recombinant hemoglobin. Blockade of nitric oxide inhibition produces a dramatic increase in the propagation velocity of esophageal contractions. In the smooth muscle of the esophagus, nitric oxide-medicated inhibitory neurones mainly control the timing, and therefore the propagation velocity, of esophageal contractions, where as cholinergic excitatory neurones mainly determine the strength of the contraction.

In the case of GERD, a substantial number of patients have ineffective propagation of the peristaltic wave as well as reduced amplitude of the primary peristaltic wave. This decrease in amplitude corresponds directly to the severity of oesophagitis. In addition, patients with GERD have higher thresholds for induction of secondary peristalsis than patients without GERD.

In line with the pharmacological basis of esophageal peristalsis, cholinergic stimulation improves the disordered motility and clearance of patients with GERD. This stimulation can be produced either by bethanechol, which stimulates cholinergic receptors, or by cisapride and erythromycin, which act on receptors in the amplitude of esophageal contractions, a decrease in the propagation velocity of the peristaltic contractions, and an improvement in esophageal clearance and transit time. In both normal subjects and GERD patients, bethanechol increases the amplitude of peristalsis, decreases the progression velocity of peristalsis, and improves esophageal transit and clearance. Bethanechol's effect on propulsive force is unknown, although it does increase the amplitude of secondary esophageal peristaltic contraction.

Cisapride increases the amplitude and propagation velocity of peristalsis in normal patients and those with GERD. It accelerates the axial propagation and increases the overall contraction lengths of the peristaltic wave. However, it has not been found to reduce the rate of failed primary peristalsis in severe GERD patients. The clearance time of postprandial reflux in GERD is decreased by cisapride; however, the effect of cisapride on secondary esophageal peristalsis has not been studied extensively. Erythromycin does not affect the amplitude of peristalsis in normal patients or GERD patients, but does reduce the progression velocity and tends to improve peristaltic performance in GERD. The effects of erythromycin on propulsive force and secondary contractions are unknown.

All these motility drugs are less effective in severe cases of reflux esophagitis when nerves and/or muscles are diseased.

SPHINCTER MECHANISM AT GASTROESOPHAGEAL JUNCTION

The movement of gastric contents into the esophagus is prevented by the sphincteric mechanism at the gastroesophageal junction (GEJ), the major antireflux barrier. The intraluminal pressure at the GEJ determines the strength of this antireflux barrier. Recent studies indicate that the smooth muscles of the lower esophageal sphincter (LES) and skeletal muscles of the crural diaphragm contribute to the GEJ pressure. Because the LES and crural diaphragms are anatomically superimposed on each other, the intraluminal pressure measurement alone

cannot distinguish between the contributions from the two structures. The evidence of the contribution of the crural diaphragm to the GEJ pressure requires simultaneous recordings of GEJ pressure and EMG of the crural diaphragm.

The pressure at the GEJ varies during inspiration and expiration. The end expiratory pressure is caused by the smooth muscles of the LES, and the inspiratory increase is caused by the active contraction of the crural diaphragm. This latter observation has been confirmed in animal studies as well as human studies. The increase in the GEJ pressure during inspiration is directly proportional to the force of inspiration, or in other words, the force of the crural diaphragm contraction. The LES and crural diaphragm reflexively contract to a number of other stimuli. Increases in intra-abdominal pressure, caused by either abdominal compression or straight-leg raises, cause reflex contractions of the crural diaphragm. The LES also reflexively contracts in response to increased intra-abdominal pressure. The LES pressure also is related to gastric motility and increases with its migrating motor complex (MMC) activity. The LES pressure is at its peak during phase 3 and lowest during phase 1 of the MMC activity. It is reasonable to assume that the increase in LES pressure during phase 3 of the MMC activity is required to counteract the increase in gastric pressure caused by gastric contraction.

GASTROESOPHAGEAL MOTOR EVENTS THAT FACILITATE GASTROESOPHAGEAL REFLUX

The ability to monitor LES pressure continuously using a Dent sleeve has greatly expanded our knowledge of the motor events associated with episodes of GER. Initial studies by Dent et al., and subsequently a number of investigators, have shown that the prerequisite for GER to occur is low LES pressure. This low LES pressure can be caused by either a defective basal LES tone or more commonly by a transient inhibition of the normal LES tone. The latter has been given the name of transient LES relaxations. The characteristics of transient LES relaxation differ from the swallow-associated LES relaxation as follows: (1) transient LES relaxation is usually longer than 10 sec in duration compared with a swallow-associated LES relaxation that is 7 to 8 sec, and (2) transient LES relaxation is not associated with a full oropharyngeal event as documented by an absence of full pharyngeal contraction or mylohyoid EMG complex. However, a partial pharyngeal contraction and/or a small mylohyoid EMG complex can be identified at the onset of 30 percent to 50 percent of the transient LES relaxations. The pathogenetic implications of defective basal tone differ from transient LES relaxation. A defective basal LES tone implies a myogenic defect and GER under this setting is a passive process that occurs because of a normally present gastroesophageal pressure gradient that is 4 to 6 mm Hg in the end expiratory state and 10 to 12 mm Hg during a tidal inspiration. On the other hand, transient LES relaxation is an active inhibition of the preexisting LES tone and implies a defective neurogenic control. It appears that transient LES relaxation is mediated through the brain stem via the vagus nerve.

Recent studies suggest that transient LES relaxation, even though initially thought to be an isolated event in the LES, is associated with a number of other excitatory and inhibitory motor events. The excitatory events can be recognized in the esophagus and usually observed as a localized or diffuse simultaneous esophageal contraction. The crural diaphragm remains relaxed during transient LES relaxation, and one may also note inhibition of gastric tone. It appears that transient LES relaxation is a response to a programmed set of events in the central nervous system, most likely in the brain stem. However, a cortical influence must be necessary because transient LES relaxation is absent during sleep.

The myogenic defect in the LES causing a defective basal LES tone is classically observed in scleroderma and is thought to be caused by atrophy of the smooth muscles. However, the reason for a defective basal LES tone in the common variety of reflux disease is not known. The defect in basal tone is either in the form of a persistently low LES pressure or a gradual drifting of normal tone to low pressures for periods of 30 to 60 seconds or longer. It is possible that the defective basal tone in the common variety reflux disease may result from the damage caused by reflux esophagitis. The healing of esophagitis by omeprazole does not improve the basal LES tone, an argument against that theory. Nevertheless, it is possible that LES muscle, once damaged, may not be able to recover. Another theory is that a certain few percent of people are born with a weak or defective LES pressure — hence reflux of infancy, and this, in turn, predisposes adults.

It appears that only a minority of patients with GER disease have a defective basal tone. These patients tend to have severe esophagitis. More commonly, transient LES relaxation is identified as the mechanism for GER that implies a defective neural control. However, it is difficult to think of transient LES relaxation as a manifestation of a neurogenic defect because it is the mechanism for belching and can be recorded fairly frequently in normal healthy individuals. A given patient may reflux exclusively by either the mechanism of transient LES relaxation or defective basal LES tone. However, there are some patients in whom both mechanisms of reflux are operative.

What is the stimulus for transient LES relaxation? Two sites that have been implicated are gastric distention and mechanical stimulation of the pharynx. The observation that transient LES relaxations and GER occur more frequently in the postprandial period suggest that gastric distention is important. Furthermore, gastric distention by a balloon increases the frequency of transient LES relaxation. On the other hand, transient LES relaxation can be recorded fairly frequently on an empty stomach and the frequency of transient LES relaxation is not consistently higher after a meal. We have recently observed that a catheter in the pharynx increases the frequency of transient LES relaxation, suggesting a role for pharyngeal receptors as the site of stimulus. A number of questions regarding transient LES relaxations remain unanswered: (1) Does the frequency of transient LES relaxation account for the difference between a normal subject and a patient? (2) What pharmacology explains the stimulus for transient LES relaxation? (3) If there were no manometric catheters and pH probes traversing the pharynx, would transient LES relaxation be recorded as the major mechanism of GER?

WHAT IS THE RELATIONSHIP OF DELAYED GASTRIC EMPTYING TO GERD?

Gastric stasis may contribute to the pathogenesis of reflux disease by increasing all of the following factors: postprandial gastric distension, volume of intragastric content available for reflux, gastroesophageal pressure gradient and frequency of transient lower esophageal sphincter relaxations (TLESRs).

About 80 percent of patients with endoscopy or ph-metry-proven GERD have vomiting or other dyspeptic symptoms (postprandial satiety, fullness, bloating, epigastric pain, belching nausea, and even vomiting) suggestive of gastric stasis. However, the predictive value of these symptoms for the presence of documented gastric stasis is very poor. Scintigraphic studies (or other validated methods for the measurement of gastric emptying) are, therefore, the only reliable way of evaluating the frequency of gastric stasis in GERD. Among 20 studies including 670 patients, in which objective evaluation of gastric emptying was performed, 14 concluded that a significant delay in gastric

emptying was present in GERD patients. Among 10 studies that considered the emptying of both solids and liquids, three concluded that there was no delay in gastric emptying, four that stasis was present for liquids and solids, two that stasis was present for solids only, and one that stasis occurred with liquids only. In summary, our data indicate that gastric stasis was found in about 40 percent of patients with GERD, and solids are mainly affected.

In most published studies, there is no clear correlation between the presence and intensity of gastric stasis and the presence and severity of the reflux, or between the lower esophageal sphincter pressure and the intensity of the stasis. However, Miscali et al. have found a linear relationship between the severity of oesophagitis and the delay in gastric emptying.

In a therapeutic study of the cause and effect relationship between stasis and reflux, the prevalence of stasis was higher in patients resistant to medical treatment. However, it has been shown that erythromycin improves gastric emptying but has no effect on esophageal acid exposure. Rather than being a causal factor, gastric stasis could therefore be an associated disorder in patients with GERD. In clinical practice, gastric emptying studies are important in the management of GERD patients not responding to medical therapy and when surgery is being considered.

WHAT IS THE RELATIONSHIP BETWEEN TRANSIENT LOWER ESOPHAGEAL SPHINCTER RELAXATIONS AND DELAYED GASTRIC EMPTYING?

In normal patients, only 30 percent of TLESRs are associated with acid reflux. This proportion increases to about 60 percent in patients with reflux disease. Postprandially, there is an increase in the frequency of TLESRs that is more pronounced in patients with reflux disease. Experimental studies have shown that gastric distension is a potent trigger for TLESRs, and in this respect, the cardia is more sensitive to gastric distension than the distal stomach. It is possible that there are differences in the behavior of the proximal stomach between patients with GERD and normal subjects, and the pressure of a hiatus hernia altering the fundic stretch receptor thresholds could be the explanation.

As well as emptying from the stomach as a whole, recent studies suggest that there is abnormal retention of both solids and liquids in the proximal stomach. A correlation between the number of postprandial TLESRs and the amount of material retained in the proximal stomach has been demonstrated. Fundoplication has been shown to improve proximal gastric emptying of solids and liquids in addition to reducing the number of TLESRs. Therefore, there is some preliminary evidence that delayed gastric emptying is associated with an increase in the number of TLESRs.

WHICH OF THE PHARMACOLOGICAL EFFECTS OF CISAPRIDE REALLY CONTRIBUTE TO ITS EFFICACY IN TREATING GERD?

Clinical pharmacological studies in healthy volunteers and patients with GERD have shown that cisapride has a wide range of pharmacological effects on the upper gastrointestinal tract. These include:

- Increase in fasting and postprandial lower esophageal sphincter pressure.
- Stimulation of esophageal peristalsis (increase in number, duration and amplitude of esophageal waves and in propagation velocity).
- Increase in propulsive force after distension.
- Stimulation of salivary secretion (volume and buffer capacity).

- Improvement in esophageal clearance and emptying.
- Reduction in distal esophageal exposure to acid.
- Improvement in gastric motility and emptying.

The extent and duration of each of the pharmacological effects of cisapride depend on the experimental conditions under which they are studied. The main reasons for the discrepancies in findings are different methodologies and different selection criteria for the subjects investigated.

The reduction in esophageal exposure to acid, which allows symptomatic improvement and mucosal healing, is clearly a result of increased esophageal clearance due to the stimulation of esophageal peristalsis and salivary secretion as well as to the increase in sphincter resistance. Esophageal exposure to acid seems to depend on the gastric emptying rate and gastric emptying is often delayed in patients with GERD. In GERD patients with delayed gastric emptying, the pH is less than 4 for longer than in patients whose emptying rate is normal. In patients with gastric motor derangement, a significant correlation was found between the emptying half-life and the reflux time. Similarly, in a group of patients undergoing antireflux surgery, those with delayed gastric emptying had a significantly higher esophageal exposure to acid than did patients without gastric motor derangement.

Administration of cisapride before meals significantly accelerated gastric emptying of solids in both healthy individuals and patients with GERD. The postprandial esophageal exposure to acid was significant in the subgroup of patients with a delayed emptying rate. The same holds true for the duration of reflux episodes. Therefore, cisapride accelerates gastric emptying in reflux patients and strongly reduces esophageal exposure to acid. This last effect is particularly evident in patients with delayed gastric emptying, probably because of the ability of the drug to correct both esophageal and gastric motor disorders.

To summarize, the stimulation of both esophageal and gastric motility is an important determinant of cisapride efficacy in GERD. The improvement of esophageal clearance, the increase in sphincter resistance, and the acceleration in gastric emptying, with a consequent reduction in the gastric volume available for reflux, all contribute to the reduction of esophageal exposure to acid, which ultimately allows symptomatic relief and mucosal healing.