An Ambulatory Bilirubin Monitoring Device for Duodenogastroesophageal Reflux

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Reflux of duodenal contents into the stomach is a normal physiological event occurring most commonly at night[1] but also in the fasting and postprandial daytime periods.[2] Previously, the terms "bile reflux" and "alkaline reflux" have been used to describe this process. However, duodenal contents contain more than just "bile" and studies have shown that the term "alkaline reflux" is a misnomer since pH > 7 does not correlate with reflux of duodenal contents.[3] Therefore, duodenogastroesophageal reflux (DGER) may be a more appropriate term to describe the pathological regurgitation of duodenal contents through the pylorus into the stomach with subsequent reflux into the esophagus.

Although, the role of acid and pepsin in causing esophageal mucosal injury is well established in both animal and human studies (Fig. 1), the importance of DGER is not clear. Animal studies show that conjugated bile acids, the predominant bile constituent in DGER, produce esophageal mucosal injury at an acidic pH; while unconjugated bile acids and the pancreatic enzyme trypsin cause mucosal injury at more neutral pH values (Fig. 1). Some extrapolate these animal studies to suggest that increased esophageal exposure to DGER, especially after acid suppression by H2-blockers or proton pump inhibitors, may lead to the development of complicated GERD including Barrett's esophagus and adenocarcinoma of the esophagus[4] in humans. However, the clinical importance of DGER in the absence of acid reflux in patients with esophageal mucosal injury remains controversial. This may be because there is no "gold standard" for detecting DGER in humans.

METHODS FOR MEASURING DGER

Various direct and indirect methodologies are employed for measuring DGER, including endoscopy, aspiration studies (both gastric and esophageal), scintigraphy, ambulatory pH monitoring, and most recently, ambulatory bilirubin monitoring

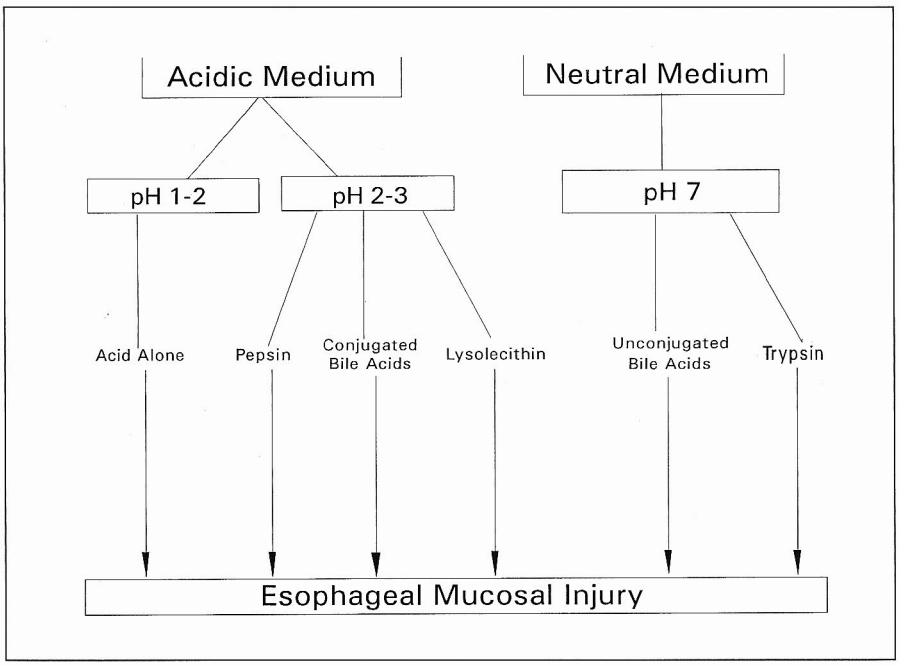

Figure 1. Postulated agents responsible for esophageal mucosal injury.

Table 1. Advantages and disadvantages of the currently available methods for detecting duodenogastroesophageal reflux (DGER).

METHOD	ADVANTAGES	DISADVANTAGES
Endoscopy	• Easy visualization of bile	• Poor sensitivity/specificity/ positive predictive value • Requires sedation • High cost
Aspiration studies	• Less invasive than endoscopy • No sedation • Low cost	• Short duration of study • Requires familiarity with enzymatic assay for BA*
Scintigraphy	• Noninvasive	• Semiquantitative at best • Radiation exposure • High cost
pH monitoring	• Easy to perform • Relatively noninvasive • Prolonged monitoring • Ambulatory	• pH > 7 not a marker for DGER • Not specific for DGR
Bilirubin monitoring (Bilitec)	• Easy to perform • Relatively noninvasive • Prolonged monitoring • Ambulatory • Good correlation with gastric BA concentrations	• Current design underestimates DGER by about 30% in acidic medium (pH < 3.5) • Requires modified diet

* BA = bile acid

(Bilitec 2000). As summarized in Table 1, these tests have their strengths and shortcomings; however, reviewing some of the human studies using these tests helps better appreciate the role of DGER in causing esophageal mucosal injury.

Endoscopy

Bile is frequently seen in the stomach and esophagus of patients during endoscopy; however, studies indicate that this observation is a poor indicator of DGER.[5,6] Recently, Nasrallah et al.[5] evaluated 110 patients with bile-stained gastric mucosa at endoscopy and found no correlation between the gastric bile acid concentrations, degree of histologic injury, or severity of endoscopic changes, suggesting that there was little clinical importance to bile-stained mucosa at endoscopy. Similarly, using scintigraphy and gastric pH monitoring to assess DGER, Stein et al.[6] found poor sensitivity (37%), specificity (70%), and positive predictive value (55%) for endoscopy in the diagnosis of excessive DGER.

Aspiration Techniques

One of the earliest methods used for evaluating DGER was the aspiration of gastric (or esophageal) contents with fluid analysis for bile acids. This technique allows direct detection of duodenal contents (bile acids and trypsin) with enzymatic or chromatographic measurements. Using this technique, recent studies[7,8] indicate that fasting bile acid concentrations may be increased in a graded fashion across the GERD spectrum, being highest among patients with Barrett's esophagus (Fig. 2). However, the reports using aspiration techniques in detecting DGER have been criticized because of short aspiration periods and the limitations of the technique, in part because previous enzymatic measurements of bile acids, commonly studied in the postprandial periods, are now known to be inaccurate.[9]

Scintigraphy

Scintigraphic studies show that DGER is a common phenomenon in normal individuals postprandially,[10] requiring that the evaluation of abnormal DGER be quantitative. Radionuclide techniques offer a noninvasive method for studying DGER; however, they have shown conflicting results. Matikainen et al.[11] found no difference in the scintigraphic amount of DGER between 40 patients with esophagitis (10% scintigraphic reflux) and 150 healthy controls (14% scintigraphic reflux). However, Waring et al.[12] reported that patients with Barrett's esophagus, especially those with complicated Barrett's, had more frequent DGER detected by 99mTc DISIDA scintigraphy than healthy volunteers.

Ambulatory Prolonged pH Monitoring

Until recently, the most popular method for detecting DGER was ambulatory 24-hour pH monitoring. Using this technique, Pellegrini et al.[13] introduced

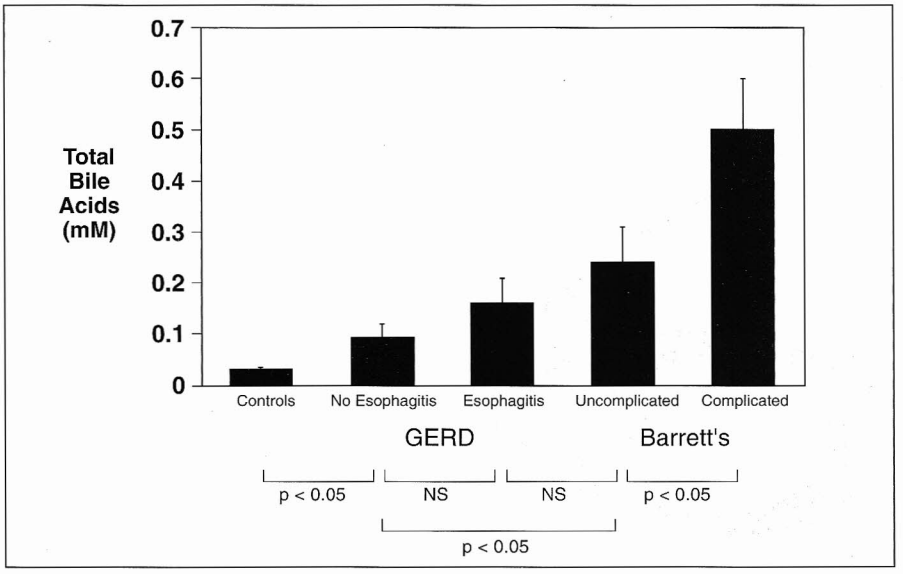

Figure 2. Mean fasting gastric bile acid concentrations in GERD spectrum.

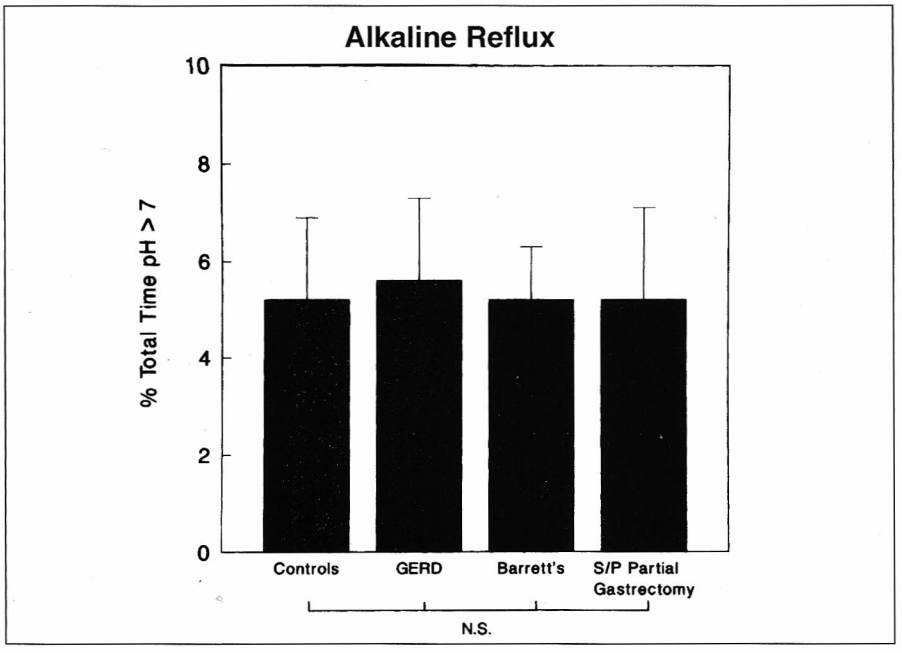

Figure 3. Mean % total times pH > 7 in GERD and partial gastrectomy patients.

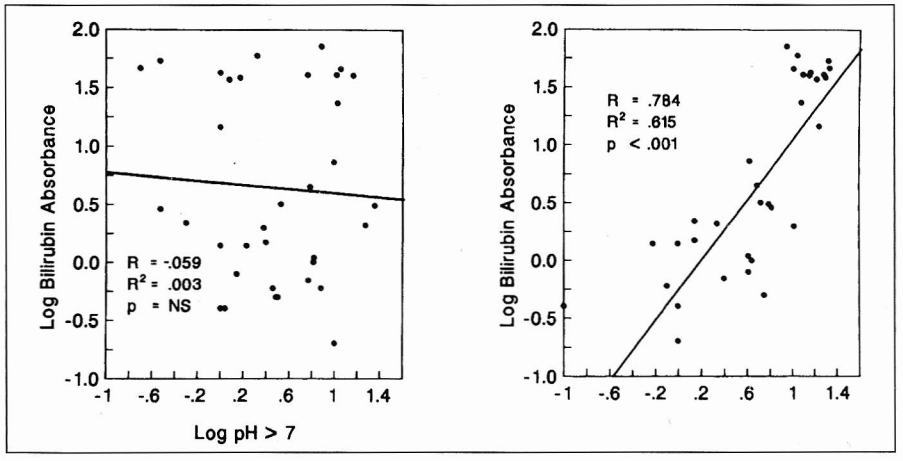

Figure 4. Relationship between DGER (bilirubin reflux) and pH > 7.

the term "alkaline" reflux, suggesting that pH > 7 be used as an indirect marker for DGER. Subsequently, Atwood et al.[4] reported that "alkaline" reflux was greater in patients with Barrett's esophagus when compared to patients with esophagitis or normal controls. Furthermore, they found that pH > 7 was significantly higher in complicated Barrett's patients (stricture, ulcer, dysplasia) than in Barrett's patients without complications, while pH < 4 did not distinguish the two groups. Therefore, the authors suggested that prolonged exposure to duodenal contents alone may promote the development of complicated Barrett's esophagus and even adenocarcinoma.

However, the measurement of esophageal pH > 7 as a marker of DGER is confounded by several problems. Precautions must be taken to use only glass electrodes, a dietary restriction of foods with pH > 7, the inspection of patients for periodontal disease, and dilation of strictures to avoid pooling of saliva. Additionally, Gotley et al.[14] found no relationship between "alkaline" exposure time and esophageal bile acids or trypsin. Similarly, Mattioli et al.,[15] using a triple-probe pH monitor placed in the distal esophagus, fundus and antrum, found that "alkaline" reflux, defined as a rise in pH > 7 from the antrum to the esophagus, was extremely uncommon. Singh et al.[16] and DeVault et al.[17] confirmed these observations by reporting that increased saliva production or bicarbonate production by the esophageal submucosal glands were the most common causes of esophageal pH > 7. Finally, using an ambulatory bilirubin monitoring device combined with pH monitoring, Champion et al.[7] reported no difference in the degree of percentage total time pH > 7 in patients with GERD, Barrett's esophagus, or partial-gastrectomy patients (Fig. 3). Furthermore, they found no correlation between esophageal pH > 7 and bile reflux into the esophageal lumen (Fig. 4), suggesting that the term "alkaline" reflux was a misnomer and should not be used when referring to DGER.

Ambulatory Bilirubin Monitoring (Bilitec 2000)

Recently, a new fiberoptic spectrophotometer (Bilitec 2000, Synectics, Stockholm, Sweden) was developed which detects DGER in an ambulatory setting, independent of pH (Fig. 5).[18] This system utilizes the optical property of bilirubin, the most common pigment in bile. Bilirubin has a characteristic spectropho-

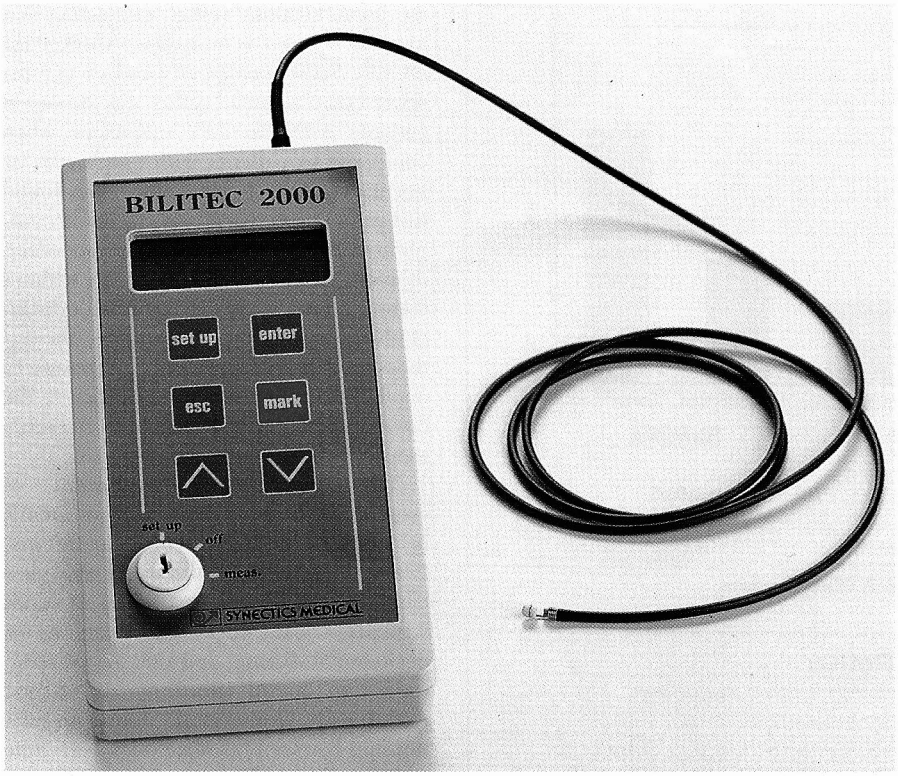

Figure 5. Ambulatory bilirubin monitoring device (Bilitec 2000)

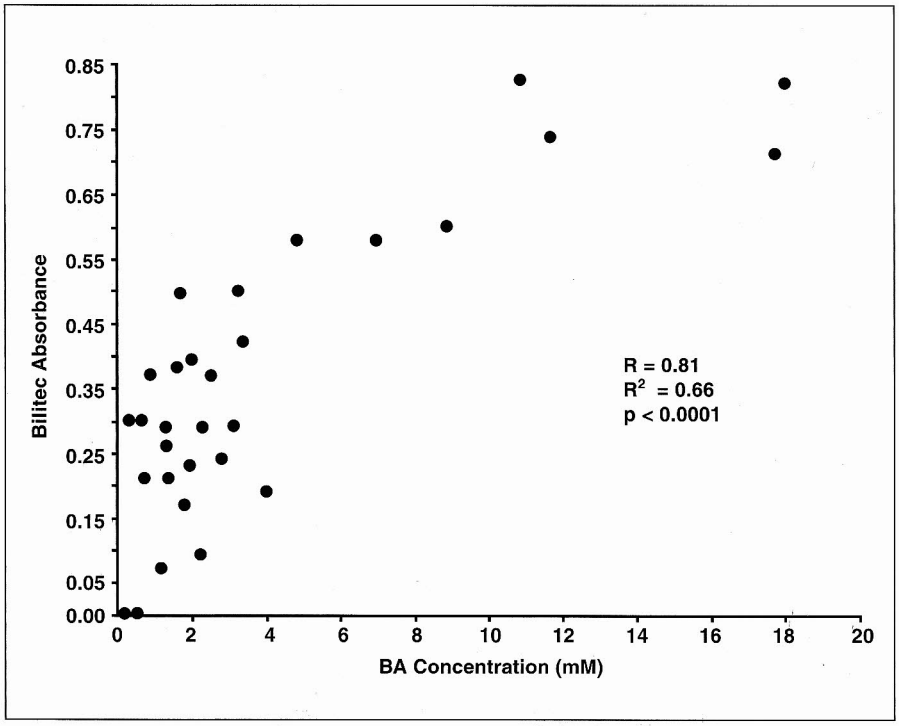

Figure 6. Bilitec absorbance readings and gastric bile acid (BA) concentrations.

tometric absorption band at 450 nm. The basic working principal of the system is that an absorption near this wavelength implies the presence of bilirubin and therefore represents DGER.

The system consists of a miniaturized fiberoptic probe which carries light signals into the probe tip and back to the optoelectronic system via a plastic fiberoptic bundle. The Teflon probe head is 9.5 mm in length and 4 mm in diameter. There is a 2.0 mm open groove in the probe across which two wavelengths of light are emitted and material sampled. Two light emitting diodes at 470 and 565 nm represent the sources for the measurement of bilirubin and the reference signals, respectively. The portable photodiode system converts the light into an electrical signal. After amplification, the signals are processed by an integrated microcomputer, and the difference in absorption between the two diodes is calculated, representing bilirubin absorption in the samples of DGER. The period between two successive pulses from the same source, representing sampling time, is 8 seconds. In addition, the software averages between the absorbances calculated over two successive samplings in order to decrease the noise of the measurements. A total of 5,400 sample recordings may be stored during a 24-hour period.

Studies from Dr. Bechi's laboratory[18] as well as our laboratory,[19] show a good correlation between Bilitec readings and bile acid concentration measurements of gastric aspirates using enzymatic assays ($R = 0.71$, $p < 0.01$ and $R = 0.82$, $p < 0.001$, respectively) (Fig. 6). Furthermore, our studies show that Bilitec readings correspond to bile acid concentrations in the range of 0.01–0.60 mM, which are more representative of bile acid concentrations found in the human stomach (0.1–1.0 mM). However, due to limitations inherent to Bilitec, it is only a semiquantitative means of detecting DGER.

Validation studies by Vaezi et al.[19] found that this instrument underestimates bile reflux by at least 30% in an acidic medium ($pH < 3.5$). In solutions with $pH < 3.5$, bilirubin undergoes monomer to dimer isomerization which is reflected by the shift in the absorption wavelength from 453 nm to 400 nm (Fig. 7). Since Bilitec readings are based on the detection of absorption at 470 nm, this shift results in underestimation of the degree of DGER. Furthermore, a variety of substances may result in false positive readings by the Bilitec, since it indiscriminately records any substance absorbing around 470 nm. This necessitates use of a modified diet to avoid interference and false readings.[18] Also, it is important to remember that Bilitec measures reflux of bilirubin and not bile acids, thereby presuming that the presence of bilirubin in the refluxate is accompanied by other duodenal contents. Although this is true in most cases, a few medical conditions (Gilbert's and Dubin-Johnson syndromes) may result in disproportionate secretion of bilirubin as compared to other duodenal contents, especially bile acids.

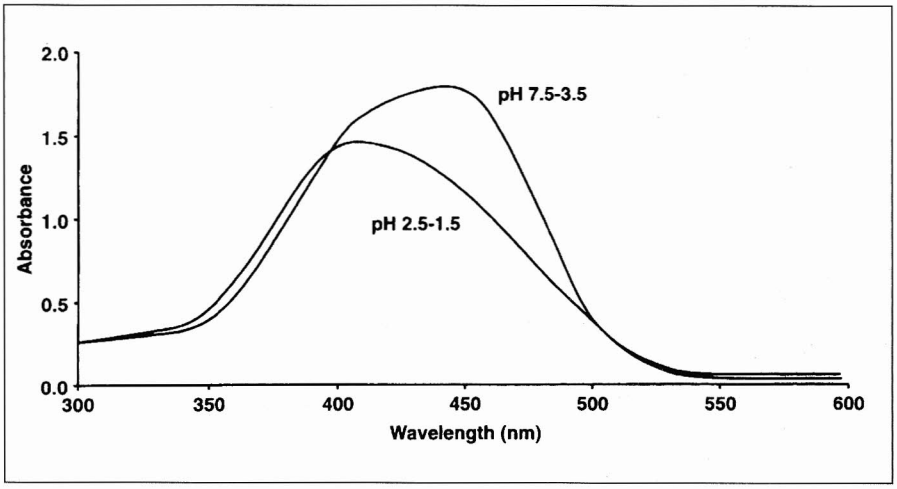

Figure 7. Spectrophotometric absorbance of bilirubin at different pH values.

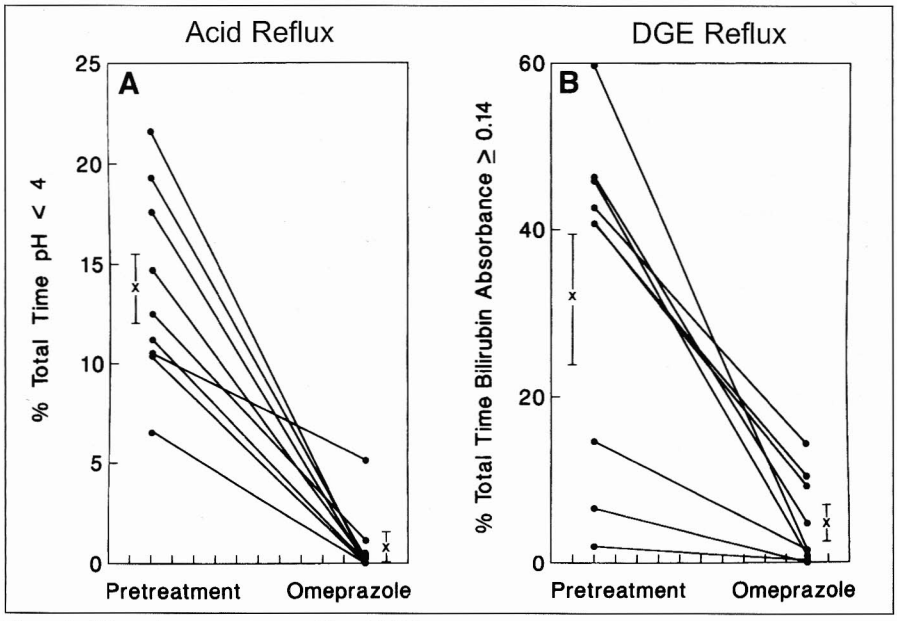

Figure 8. Effect of omeprazole on acid and DGER.

CLINICAL STUDIES WITH BILITEC

Despite its limitations, Bilitec is an important advancement in the assessment of DGER in the clinical arena. Several studies using this new device have provided important insight regarding the role of DGER in causing esophageal mucosal injury in humans. Recently, Champion et al.[7] found a significant graded increase in both acid and DGER from controls to esophagitis patients, with the highest values observed in patients with Barrett's esophagus. Similar observations were made by Vaezi et al.[8] in patients with and without complications of Barrett's esophagus. They found that both groups of Barrett's patients had significantly greater quantities of acid and DGER than controls. More importantly, reflux of acid paralleled DGER (Fig. 4), and both were significantly higher in patients with complicated Barrett's than the uncomplicated group. The results in these two studies have recently been confirmed by two other groups.[20,21] Furthermore, studies by Vaezi et al.[22] found that simultaneous esophageal exposure to both acid and DGER was the most prevalent reflux pattern occurring in 95% of patients with Barrett's esophagus and in 79% of GERD patients. Thus, these studies support the findings in animal data, suggesting a possible synergy between acid and DGER in the development of esophagitis and Barrett's esophagus.

However, the role of DGER in producing esophageal mucosal injury, in the absence of reflux, was not clarified until recently. Sears et al.[23] studied 13 partial gastrectomy patients with reflux symptoms and found increased DGER by Bilitec monitoring in 77% of patients. However, endoscopic esophagitis was only present in those with concomitant acid reflux. Additionally, Vaezi et al.[24] recently showed that 24% of upper GI symptoms reported by partial gastrectomy patients was due to DGER in the absence of acid reflux. Therefore, these studies underscore the important point that DGER, without abnormal amounts of acid reflux, may cause reflux symptoms but does not usually result in esophageal mucosal injury in humans.

Bilitec has also been used to study the effects of drug therapy on DGER. Recent studies by Champion et al.[7] using Bilitec in patients with severe GERD found that aggressive acid suppression with omeprazole (20 mg BID) dramatically decreased both acid and DGER (Fig. 8). Although not specifically studied, the authors speculated this was due to omeprazole's inhibition of both gastric acidity and volume. This finding has important implications for treating patients with both acid and DGER, suggesting that medical therapy may decrease both constituents to a similar degree as anti-reflux surgery. Furthermore, the higher intragastric and intraesophageal pH environment created by the proton pump inhibitors inactivate conjugated bile acids, the main DGER ingredients implicated in causing esophageal mucosal injury.[25] In patients who have upper GI symptoms due to non-acidic DGER, a recent double blind cross-over study[26] found that cisapride (20 mg qid) significantly reduces both DGER measured by the Bilitec and the associated upper GI symptoms in partial gastrectomy patients. Thus, medical therapy with this promotility drug is an alternative to surgical Roux-en-Y diversion in this difficult group of patients.

Summary

Both animal and human studies convincingly show that acid is the key agent in causing esophageal mucosal injury. However, recent studies, using an advanced technique to measure DGER spectrophotometrically and independent of pH (Bilitec 2000), found that duodenal contents often are present in the esophageal refluxate. The degree of esophageal exposure to acid and DGER showed a graded and similar increase from controls to esophagitis patients, with the highest values observed in patients with Barrett's esophagus. This close relationship raises the possibility that synergistic actions of acid, pepsin, and conjugated bile acids may

be contributing to the development of Barrett's metaplasia and possibly even adenocarcinoma. On the other hand, recent human studies using the Bilitec 2000 show that DGER in non-acidic environments (i.e., partial gastrectomy patients) may cause symptoms but does not cause esophageal mucosal injury. Both medical and surgical therapy can prevent DGER. Proton pump inhibitors decrease the volume of gastric contents available to reflux into the esophagus and raise intragastric pH, thereby inhibiting conjugated bile acids. The promotility agent cisapride decreases DGER by increasing LES pressure and improving gastric emptying. Antireflux surgery prevents DGER by improving LES function while Roux-en-Y diversion prevents the reflux of duodenal contents into the stomach and esophagus. **STI**

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