Technical aspects and clinical indications of 24-hour intragastric bile monitoring.

Original Paper

Technical Aspects and Clinical Indications of 24-Hour Intragastric Bile Monitoring

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KEY WORDS: Bile reflux; Duodenogastric reflux; Reflux monitoring
ABBREVIATIONS: Lower Esophageal Sphincter (LES); Duodenogastric Reflux (DGR)

SUMMARY

Bilitec 2000 is a new device which spectrophotometrically detects the presence of bilirubin in the refluxate. It is, up to date, the only method able to monitor for 24 hours the exposure time of esophageal and/or gastric mucosa to bilirubin-containing reflux. From the technical point of view, a particularly relevant aspect is the necessity of associating pH and Bilitec monitorings. The reason why is that, even in the stomach where Bilitec itself is adequate for assessing the exposure time to duodenogastric reflux, the damaging capability of the different components of reflux strictly depends upon pH. The most correct position inside the stomach for gastric monitoring is the 5cm-below-the-LES-distal-border-position. The diet needs to be standardized in order to avoid false positive results due to the ingestion of foods with absorption close to bilirubin absorption. Ranges of normality will soon be available from a collaborative European Study. At variance with the indications for esophageal monitoring which are wide (the same as for pH-monitoring), indications for gastric Bilitec monitoring are represented only by severe dyspeptic symptoms possibly related to duodenogastric reflux. An antrum-confined C gastritis in the absence of history of consumption of gastro-lesive drugs strongly suggests the possibility of duodenogastric reflux. In this case, Bilitec monitoring can provide further evidence by measuring the time of exposure of the gastric mucosa to reflux.

INTRODUCTION

Duodenogastric reflux (DGR) has been considered responsible for a variety of foregut diseases (see other papers of the present issue of Hepato-Gastroenterology). However, none of the many different techniques, which have been proposed for its detection in the past, is entirely satisfactory. Gastric pH-monitoring is an indirect technique and is not capable of reflux detection in achlorhydric or hypochlorhydric stomachs and in the post-prandial period. Cholescintigraphy and other types of scanning are stationary methods and require the consumption of radioactive reflux markers. Bile acid quantitation in the gastric aspirates, in addition to being discontinuous, needs the removal from the stomach of what should be simply measured. Furthermore, most of these methods restrict data samplings to short periods. The unsatisfactory results of all these techniques have pushed the development of Bilitec 2000. This is an internationally patented new device, which spectrophotometrically detects the presence of bilirubin in the refluxate due to bilirubin characteristic absorption peak at 450 nm (1,2). Bilitec 2000 allows 24-hour continuous esophageal and/or gastric monitoring of bilirubin-containing reflux. Although it cannot be considered a perfect method, to date it appears to be the best method available in order to monitor the exposure time of esophageal and/or gastric mucosa to bilirubin-containing reflux (3-6). Validation studies from different groups have confirmed Bilitec's effectiveness in duodenogastric reflux detection (4,7,8).

Hepato-Gastroenterology 1999; 46:54-59

TECHNICAL GUIDELINES FOR SUCCESSFUL BILITEC MONITORING

Calibration of the Probe

Before each test, calibration is performed. This is a very simple maneuver as it consists of introducing the tip of the probe into a suitable water-containing "black box" and assuming the stabilized absorbance value as zero. The use of the "black box" is always necessary in Bilitec *in vitro* evaluation of samples either containing or not containing bilirubin in order to avoid photocomposition and light scattering phenomena. No other points at higher absorbance values need to be determined. However, it is advisable to repeat calibration at the end of the monitoring to be sure that no technical problems have taken place. The measurement period of Bilitec is 1 second. In addition, the software averages between the absorbances calculated on successive samplings. Three options for the sampling time are available: 4, 8, and 16 seconds. Each sampling value, therefore, represents the average of 4, 8 or 16 measurements, respectively. Usually, a sampling time of 4 seconds is used.

Association with pH-monitoring

What we recommend is that even in the stomach, where Bilitec by itself is adequate for assessing the exposure time of gastric mucosa to DGR, Bilitec monitoring should be associated with pH-monitoring. The reason for this is that the damaging capability of the different components of DGR strictly depends upon pH (9-12). Therefore, the association of the two monitorings with the tips of the two probes placed in the same site provides wider information. Particularly, with the association of the two monitorings, not only the exposure time but also the probability of mucosal damage, which is pH-dependent, will be known.

Placement of the Probe

At variance with what happens for esophageal measurements (position of the probe: 5cm above the upper limit of LES), there is no agreement concerning the position of the probe inside the stomach. The best site for monitoring DGR appears to be represented by the body between its vertical and horizontal parts. This is because this position seems to be the most appropriate in order to prevent the probe from slipping into the duodenum and so as not to miss the detection of the antrum-limited refluxes during the 24-hour period. However, the placement of the probe in this position requires fluoroscopy, which should also be used in order to check the probe position at the end of the exam. Furthermore, even though fluoroscopy is helpful, sometimes it is impossible to reach and maintain this position since the tip, after hitting the gastric wall, may turn backwards into the fundus. This results in heterogeneous and non-comparable sites of monitoring in different subjects and implies difficulties in establishing reference values. An alternative to this monitoring site is represented by the 5cm-below-the-LES-distal-border-position. Although this site of monitoring would probably miss the antrum-confined refluxes, two advantages possibly make this monitoring site the best one. The first advantage is that fluoroscopy is not requested as this site can easily be reached after simple esophageal manometry; the second is that the possibilities of displacement and turning back of the probe are negligible with consequent easy standardization and comparability of the 24-hour monitorings of DGR.

Standardization of Diet and Activities

Gastric as well as esophageal measurements can be affected by the ingestion of some foods (e.g., those with an absorption between 400 and 450nm). Thus, these foods should be avoided. Since it is impossible to provide a complete list of foodstuff interfering with measurements, we provide our patients with a list of recommended foods. This includes partially skimmed milk, sugar, dry biscuits, white cheese, boiled chicken breast, boiled potatoes, bananas, and apples. As an alternative to this natural diet, a fluid commercial equilibrated diet with proper absorbance characteristics can be used. At this time, a combination of the above-mentioned natural diet and commercial diet is used in our laboratory. The commercial component of the diet consists of vanilla- or banana-flavored Nutridrink by Nutricia (1000ml subdivided into three meals for a total of 1500 calories). This combination offers the advantages of the standardized high-calorie equilibrated composition of the commercial product together with the physiologic advantage of the presence of a solid component due to the natural foods. The subjects undergoing monitoring follow this strict menu subdivided into three different meals. No

foods or beverages (except for water) are allowed between meals.

The problem of the diet seems to be a major one since improper foods are capable of returning false positive results. On the other hand, the exclusion of the post-prandial periods from the evaluation of monitoring, as previously suggested in order to allow permissive diets (13), seems to give up to one of the major advantages of Bilitec monitoring when compared to gastric pH-monitoring (e.g., the possibility of assessing duodenogastric reflux episodes even in the post-prandial periods). Another problem concerning the diet is the possibility of solid food pollution of the tip of the probe; this uncommon event is easily recognized on bilimetric tracing by an out-of-scale peak followed by a persistent plateau.

As far as exercise is concerned, no restrictions are recommended. It is the presence *per se* of the device, mostly associated with the presence of a pH-monitoring device, which suggests the proper restruction of physical activities undergoing monitoring an almost uniform reduction of physical activities.

Smoking may either be allowed or not. However, since in our personal series we have requested our group of normal volunteers not to smoke, in order to obtain reference values, this should also be requested of our study subjects.

Data Interpretation

As for acid reflux at pH-monitoring, for which a conventional threshold value was indicated at pH=4, similarly for Bilitec monitoring a threshold above which the reflux is considered to be present was conventionally identified at 0.14 absorbance units. This value was selected because the combination of scattered particles in the gastric juice and background noise due to electronics can determine absorbance levels of 0.14 max (2-5). Higher threshold values have been proposed and used (e.g., 0.25) (14). However, the software (EsopHogram, Gastrosoft Inc, Texas), which goes with Bilitec's present version, allows for the selection between different threshold values and evaluation of the data accordingly. When an adequate number of normals and patients will be studied, the best threshold value will be selected on the basis of its capability to separate patients and controls optimally, although the possibility of identifying an absorbance value capable of representing a threshold for mucosal damage can hardly be envisaged. The pursuit of the latter goal could imply that thresholds for esophageal and gastric Bilitec monitoring could ultimately be different.

TABLE 1 Values for the Different Components of Duodenogastric Reflux in Normal Volunteers

Component	Normal volunteers (n=6) Median (range)
Total time %	3.8 (0.9-32.9)
Upright time %	2.3 (1.2-27.3)
Supine time %	3.0 (0.4-44.5)
Number of episodes	60.0 (33.0-247.0)
Number of episodes >5 min	1.5 (0.0-12.0)
Longest episode (min)	10.0 (3.0-91.0)

The same components, which are considered relevant at pH-monitoring for acid reflux, must also be assessed in order to evaluate 24-hour Bilitec monitoring and to discriminate physiological from non-physiological duodenogastric reflux **(Table 1)**. In addition, the EsopHogram program provides further elaboration of the data for comparison. Similarly to what has been done for pH-monitoring, a score for duodenogastric and duodeno-gastro-esophageal reflux assessed by means of Bilitec monitoring is under study.

Reproducibility of Measurements

In vitro reproducibility appeared very good (4). Only two studies have addressed the problem of the reproducibility of *in vivo* measurements. One of them assessed DGR (14) and the other duodeno-gastro-esophageal reflux (16) in the same series of subjects on 2 different days. Reproducibility in both these studies appeared acceptable with no significant differences between the basal and repeated sets of measurements.

Normal and Abnormal Values

The normal range, or rather the reference values, for a biological parameter should include all the values within that limit above or below which harmful and/or clinically relevant consequences result. However, for most parameters it is impossible to identify such a threshold on this objective basis. Therefore, what is usually done is that a particular parameter is investigated in the general population, considering as normal those values in between two extreme percentiles.

Usually, for the functional investigations of the upper gastrointestinal tract, two types of reference subjects (with respect to the parameter under study) can be used: 1) normal volunteers (i.e., subjects who volunteer for the exam; mostly hospital staff, students, nurses, or doctors); and, 2) subjects coming to the investigators' attention for a variety of diseases which do not affect the physiology of the upper gastrointestinal tract, who have a negative history for upper gastrointestinal disorders, and who give their informed consent to undergo that particular investigation.

We have, at the moment, in our laboratory in Florence studied only normal volunteers by means of 24-hour monitoring placing the probe under fluoroscopy between the vertical and the horizontal part of the gastric body with the standardization of diets and activities according to the guidelines previously reported and selecting as threshold 0.14 absorbance units. Values, which were found in 8 normal volunteers, are given in **Table 1**. A few additional normal volunteers were also studied placing the probe 5cm below the manometrically-identified LES. The latter data will be published as part of a collaborative European Study.

CLINICAL INDICATIONS FOR BILITEC MONITORING

In order to understand the indications for any kind of "bile" reflux monitoring procedure, two preliminary questions need to be answered: 1) is the reflux of bile acids, lysolecithin, and pancreatic enzymes capable of damaging gastric mucosa? and, 2) how often and under what conditions does this type of reflux take place?

With regard to the first question, from an experimental point of view it has been widely proven that biliary acids, trypsin, and lysolecithin are capable of damaging the esophageal mucosa (15) and that the mechanism by which this happens is probably the same both in the esophagus and the stomach (16). In this mechanism, the presence of an acid environment seems to play a major and multifaceted role since it is considered indispensable in creating the pH gradient which allows for intracellular concentration of bile acids capable of determining cytotoxic effects (17). Moreover, this effect of bile acids makes the mucosa leaky and permeable to H^+ back diffusion, which is capable of increasing the mucosal damage (16).

From a clinical point of view, bile acids, lysolecithin, and trypsin, which at a certain level physiologically reflux into the stomach (18,19), are capable of damaging the gastric mucosa, as has been shown by previous studies on non-operated subjects and most of all in partially gastrectomized subjects (22-24). Mucosal damage results in a peculiar type of gastritis (known as C gastritis), in which foveolar hyperplasia represents a prominent feature and is associated with reflux-determined changes in gastric mucosal proliferative activity (25). This type of gastritis is almost always present after partial gastrectomy and is considered a cancer-favoring condition. On the contrary, it can be seldom shown in the intact stomach. In the latter, it is mostly associated with particular conditions, such as previous cholecystectomy, which are known to predispose to DGR. DGR is capable of causing symptoms mainly represented by epigastric pain/discomfort (26). In addition, DGR is considered to be involved in gastric ulcer (27), C gastritis (20,21), post-gastrectomy syndromes (21-24), gastric cancer (25) and, when associated with gastroesophageal reflux, in particularly severe esophagitis (28).

Therefore, once it has been accepted on the basis of experimental and clinical evidence that DGR is capable of damage on gastric mucosa and also potentially responsible for symptoms, let us see what the clinical indications of Bilitec intragastric monitoring are. As far as the operated stomach is concerned, gastric Bilitec intragastric monitoring is not indicated, even in order to decide on a total biliary diversion operation. As a matter of fact, the latter surgical procedure in partially gastrectomized subjects is indicated only in the presence of esophagitis (endoscopically demonstrated) and/or clinically relevant bilious vomiting.

In the intact stomach, the only clinical indication of intragastric Bilitec monitoring is represented by severe dyspeptic symptoms, possibly related to DGR. These are aspecific symptoms, such as epigastric pain/discomfort, gastric fullness, etc., which require a complex diagnostic work-out in order to understand whether or not they are caused by DGR. Upper endoscopy with multiple gastric biopsies is mandatory. An antrum-confined

gastritis with the stigmata of C gastritis (foveolar hyperplasia, a paucity of inflammatory infiltrate, etc.) with a negative history for consumption of gastro-lesive drugs and especially in the absence of *Helicobacter pylori* infection strongly suggests the responsibility of DGR. In this case, Bilitec monitoring can provide further evidence by measuring the time of exposure of the gastric mucosa to DGR. Once the reference values for the exposure time will be established in normal volunteers (this step would be an important achievement even from a purely physiological point of view since the duration of the exposure time to DGR in normals is not known), they could represent an important feature to be considered when deciding upon therapeutic strategies. Particularly, Bilitec monitoring could provide important information if a total biliary diversion operation is considered. In this case, an objective demonstration of DGR seems mandatory before undertaking a duodenal switch.

It is patent from the above that the clinical indications of intragastric Bilitec monitoring are quite narrow. This is exactly the opposite of what is true for esophageal Bilitec monitoring. Indeed, no indications exist in the esophagus for pH or Bilitec monitoring alone, but simultaneous pH and Bilitec monitoring should always be performed. In the esophagus, therefore, indications for Bilitec monitoring are the same as for pH-monitoring. The main reasons for this are represented by the well-known high prevalence of mixed gastroesophageal refluxes, which can only be detected and their duration measured by the former technology. Moreover, the well-known very severe esophagitis processes, which in the past constantly followed total gastrectomy with esophago-duodenal anastomosis or simple esophago-jejunostomy (29,30), are the most certain witnesses of the damaging capability of "alkaline" reflux, independently from "acid" reflux, on esophageal mucosa.

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