

Esophageal pH testing in patients refractory to proton pump inhibitor therapy

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BACKGROUND: Proton pump inhibitors (PPIs) are the most potent drugs available for the management of gastroesophageal reflux disease (GERD). Ambulatory 24 h pH monitoring is often recommended for patients experiencing symptoms despite PPI therapy. Recent pivotal data suggest that pH studies are predictably normal in this setting, casting doubt on the clinical utility of the current practice.

OBJECTIVE: To describe 24 h pH findings in patients referred by gastrointestinal specialists for the indication of GERD refractory to PPI therapy.

METHODS: A retrospective review was performed, examining all patients undergoing ambulatory esophageal pH monitoring at the St Boniface General Hospital Motility Laboratory, between January 2002 and June 2005. Tests performed in patients clinically suspected of having GERD who were not responding to PPI therapy formed the study group. pH data were analyzed for the total, upright and supine periods. Abnormal reflux parameters were defined by applying three criteria: DeMeester score greater than 14.72; pH less than 4.0 more than 5.5% of the total time, more than 8.3% of the time upright or more than 3% of the time in the supine position; and pH less than 4.0 for more than 1.6% of the total time.

RESULTS: A total of 417 patients underwent pH monitoring during the time of the review. One hundred seven patients (mean age 51.7 years; 37 men and 70 women) met study criteria. Sixty-eight (63.6%) were referred by a gastroenterologist and 39 (36.4%) were referred by a gastroenterologist surgeon. Sixty-one patients were on twice-daily PPIs and 46 were on once-daily dosing. Using the most stringent pH criteria, namely criteria 2, pH readings were abnormal in 30% of patients on once-daily PPIs and in 25% of patients on twice-daily dosing. The prevalence of abnormal pH readings were even higher if criteria 1 or 3 were applied.

CONCLUSIONS: In a patient population assessed by a specialist as having clinically suspected GERD that is not responding to PPI therapy, a substantial number of patients will have abnormal esophageal pH test results. The role of pH testing in the algorithm of GERD is evolving; however, our data suggests that an abandonment of pH testing is premature.

Key Words: GERD; pH testing; PPIs

Gastroesophageal reflux disease (GERD) affects 35% to 40% of people in the Western world (1,2) and accounts for an economic burden exceeding that of other gastrointestinal disorders (3). Standard doses of proton pump inhibitors (PPIs), which are the most potent drugs available for the

Contrôle du pH œsophagien chez les patients réfractaires aux inhibiteurs de la pompe à protons

HISTORIQUE : Les inhibiteurs de la pompe à protons (IPP) sont les plus puissants médicaments offerts pour la prise en charge du reflux gastro-œsophagien (RGO). La surveillance ambulatoire du pH des 24 heures est souvent recommandée chez les patients qui éprouvent des symptômes, malgré un traitement par IPP. De récentes données déterminantes laissent supposer qu'il est prévisible que la surveillance du pH révèle des résultats normaux dans ce contexte, ce qui remet en question l'utilité clinique des pratiques actuelles en ce sens.

OBJECTIF : Décrire les résultats de pH des 24 heures chez des patients adressés par des gastro-entérologues pour une indication de RGO réfractaire au traitement par IPP.

MÉTHODES : Les auteurs ont procédé à une analyse rétrospective de tous les patients qui se sont soumis à une surveillance ambulatoire du pH œsophagien au laboratoire de motilité de l'Hôpital Général de St Boniface entre janvier 2002 et janvier 2005. Les patients cliniquement présumés atteints de RGO chez qui les tests ont été réalisés et qui ne répondaient pas aux IPP ont formé la population de l'étude. Les résultats de pH ont été analysés pour certaines périodes : totale, en position debout et couchée. Les paramètres du reflux ont été définis par l'application de trois critères : score de DeMeester, pH inférieur à 4,0 pendant plus de 5,5 % du temps total, pendant plus de 8,3 % du temps en position debout et pendant plus de 3 % du temps en position couchée, et pH inférieur à 4,0 pendant plus de 1,6 % du temps total.

RÉSULTATS : En tout, 417 patients ont été soumis à la surveillance du pH durant la période concernée par l'analyse. Cent-sept patients (âge moyen 51,7 ans, 37 hommes et 70 femmes) répondaient aux critères de l'étude. Soixante-huit (63,6 %) étaient adressés par un gastro-entérologue et 39 (36,4 %), par un chirurgien en gastro-entérologie. Soixante et un pour cent des patients prenaient des IPP deux fois par jour et 46 %, une fois par jour. Sur la base des normes les plus strictes en termes de pH, c'est-à-dire, le critère 2, les lectures de pH se sont révélées anormales chez 30 % des patients qui prenaient des IPP une fois par jour et chez 25 % des patients qui les prenaient deux fois par jour. La prévalence des résultats de pH anormaux était plus grande si les critères 1 ou 3 étaient appliqués.

CONCLUSION : Dans une population de patients évalués par un spécialiste pour RGO clinique présumé ne répondant pas aux IPP, un nombre substantiel de patients présenteront des résultats anormaux aux tests de pH œsophagien. En présence de RGO, le rôle du pH dans l'algorithme thérapeutique est en mutation. Par contre, selon nos données, il serait prématuré d'abandonner cette mesure.

management of GERD, are known to heal erosive esophagitis in more than 90% of patients (4). However, approximately 20% of people with GERD will continue to be symptomatic despite using double the standard PPI dose (5,6). Potential explanations are diverse and include incomplete acid suppression, the

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presence of non-acid reflux, decreased PPI bioavailability due to pharmacogenetic differences in drug metabolism and visceral esophageal hypersensitivity (7).

Ambulatory pH monitoring in patients undergoing therapy is typically recommended for those with persistent symptoms of GERD despite double-dose PPI therapy to assess whether acid suppression is adequate (8). However, recently published data indicate that pH testing is predictably normal in this setting, casting doubt on the clinical utility of performing pH tests in this setting (9).

In view of this recent report (9), we undertook a review of our experience with 24 h esophageal pH monitoring in patients with an inadequate response to PPI therapy. The objective of our study was to determine the prevalence of abnormal 24 h pH levels in patients undergoing testing for the indication of GERD that is unresponsive to PPI treatment.

METHODS

Patient population

Indications for and results of a 24 h pH test were reviewed in all patients undergoing ambulatory esophageal pH monitoring at the St Boniface General Hospital Motility Laboratory (Winnipeg, Manitoba), from January 2002 to June 2005. Patients whose tests were performed for the indication of clinically suspected GERD refractory to PPI therapy were selected and formed the study group.

The St Boniface General Hospital is a tertiary care centre located in the province of Manitoba. The laboratory performs approximately 200 pH tests per year. Requests were limited to 18 specialists, 13 of whom were gastroenterologists and five of whom were gastrointestinal (GI) surgeons. The clinical indication for testing, patient symptoms and current medical therapy were documented on a standardized form by the specialist who requested the test. All patients were assessed before the test by a dedicated GI nurse clinician to confirm the presenting symptoms, test indication and medical regimen.

Test protocol

All patients referred for a pH test received a telephone call and written reminder to comply with their medication regimen as prescribed by their referring physician. Drug compliance was again reviewed by a GI nurse clinician at the time of presentation for testing. If patients were noncompliant, a repeat appointment was arranged within seven to 10 days.

Before each test, the pH electrodes were calibrated at 37°C in two separate buffer solutions at pH 7.0 and pH 1.0, respectively. Immediately after calibration, the distal pH electrode was passed nasally and positioned 5 cm above the proximal border of the manometrically defined lower esophageal sphincter. Where a manometrically defined lower esophageal sphincter was not available, the pH step-up technique was employed (8). The pH electrodes were connected to a portable digital recorder, which stored data for 24 h.

Patients returned home for 24 h with instructions to keep a diary of all symptoms, meal times and body positions. Patients were further instructed to perform their usual daily activities without dietary restrictions, including complying with their medical regimen. Upon completion of the test, patients returned to the GI lab where the pH probe was withdrawn and the diary of all symptoms was reviewed by the GI nurse clinician.

Data were downloaded onto a personal computer for analysis using Esophagram software (Medtronic, USA). The

proportion of the total time the pH was below 4.0 was calculated, as was the proportion of time the pH was below 4.0 while supine and upright. A DeMeester score was also calculated from these data.

Definitions

Patients were classified on the basis of PPI dose (once per day or twice per day) and on the basis of the predominant symptom, whether typical (heartburn or regurgitation) or atypical (eg, cough or nasal symptoms). Abnormal reflux parameters were identified by applying three criteria:

- 1) DeMeester score greater than 14.72
- 2) a) pH less than 4.0 for more than 5.5% of the total time
b) pH less than 4.0 for more than 8.3% of all time spent in an upright position
c) pH less than 4.0 for more than 3% of all time spent in a supine position
- 3) pH less than 4.0 for more than 1.6% of the total time (8,9).

These criteria were chosen because the DeMeester score (criterion 1) was entrenched in the literature while criteria 2 and 3 were used in the study by Charbel et al (9). Implementing these three criteria allowed for a comparison between the present study and the study by Charbel et al.

The present study was approved by the ethics committees of the University of Manitoba and St Boniface General Hospital, an affiliated tertiary care institution.

RESULTS

Four hundred seventeen patients underwent 24 h ambulatory pH monitoring between January 2003 and June 2005. One hundred seven patients who underwent testing for the indication of clinically suspected GERD refractory to PPI therapy were identified. The mean age of these patients was 51.7 years and 70 (65%) were women. Sixty-one of 107 patients (57%) were using at least twice-daily PPI therapy. Sixty-three per cent of subjects were referred by a gastroenterologist and 37% were referred by a GI surgeon. Seventy-eight per cent of patients manifested typical symptoms of heartburn and regurgitation.

The most common symptom was heartburn, which was present in 72% of patients, whereas 41% complained of regurgitation. The atypical symptoms of chest pain, cough, hoarseness, sore throat and asthma were much less frequent. Chest pain was present in 21 of 107 patients (20%), cough in 19 (18%), hoarseness in 16 (15%), sore throat in 11 (10%) and asthma in six (6%).

Thirty per cent of patients in the study group had an abnormal DeMeester score, whereas 24% and 50% were classified as having an abnormal pH test for GERD based on criteria 2 and 3, respectively (Table 1). Of patients with an abnormal pH test result according to criterion 2, 77% had typical symptoms. Subjects on once-daily PPIs were not statistically more likely to have typical GERD symptoms than subjects on higher doses of PPIs (Table 2). The total esophageal acidification time for those with abnormal pH test results by criterion 2 is shown in Table 3.

DISCUSSION

Patients with suspected GERD whose symptoms do not resolve on PPI therapy are frequently referred for ambulatory pH monitoring. This clinical practice is endorsed by an American

TABLE 1
Patients with abnormal pH test results by criteria and proton pump inhibitor (PPI) dose

PPI dose	Criterion 1*	Criterion 2†	Criterion 3‡
Once-daily (n=46), n (%)	14 (30.4)	11 (24)	22 (48)
Twice-daily (n=61), n (%)	18 (29.5)	15 (24.5)	31 (51)
Total (n=107), n (%)	32 (30)	26 (24)	53 (50)

*DeMeester score greater than 14.72; †Percentage of time pH less than 4.0 (more than 5.5% of the total time, more than 8.3% of all time upright or more than 3% of all time supine); ‡pH less than 4.0 for more than 1.6% of the total time

Gastroenterological Association position paper (8). A recent study (9) has cast serious doubt regarding the validity of this approach.

In 2005, Charbel et al (9) described their experience in a retrospective review of 250 patients who underwent pH monitoring for the indication of gastroesophageal reflux symptoms refractory to PPI therapy. Of the 250 patients, 119 were on a once-daily dose of PPIs and 131 were on a twice-daily dose. Of the patients on twice-daily dosing, abnormal results were found in 1% to 9% of patients based on the criteria used. Our results differed because 24% to 50% of patients on twice-daily PPI therapy in the present study had abnormal results based on the criteria used.

The most apparent difference between the studies is that our patients represented a selected population, referred only after assessment by a gastroenterologist or GI surgeon. We believe that the specialists were able to identify the patients with non-GERD symptoms, thus eliminating those patients from our study group. The application of PPIs by a broad group of physicians has been noted to be associated with an increase in PPI failures (7). A prospective multicentre study (10) of pH monitoring in an open system indicated that the rate of appropriate pH studies was higher when requested by a gastroenterologist.

Furthermore, we do not believe that compliance with medication was an issue among our patient population, because many mechanisms were in place to minimize the effect of this potential confounding variable. Our pH probes were placed by either manometric or gastric step-up localization techniques. Both techniques are described in the literature (1,11). The gastric step-up may lead to inadvertent proximal probe placement. If this had occurred in our laboratory, the number of abnormal pH results would have been underestimated.

It has been reported that approximately 20% of GERD patients on twice-daily PPI therapy have incompletely controlled symptoms (5,6). Leite et al (5) reported that 19% of patients with reflux symptoms despite twice-daily PPI therapy, had differing gastric acid profiles from those who were asymptomatic on twice-daily PPIs. Almost all of these patients had their gastric acid profile normalized by a further increase in the PPI dosage. Unfortunately, esophageal pH profiles and symptom responses to normalizing the gastric acid profile was not reported, preventing a conclusive understanding of the clinical significance of these findings.

In a study by Spechler et al (6), 16% to 22% of GERD patients with Barrett's esophagus on high-dose esomeprazole regimens (40 mg twice per day and 40 mg three times per day, respectively) were found to have abnormal esophageal pH levels (pH less than 4.0 for more than 5.5% of the time). Similar rates of abnormal esophageal pH test results despite PPI therapy

TABLE 2
Features of patients with abnormal pH test results based on criterion 2 in Table 1

PPI dose	Total patients (n=26)	Patients with typical symptoms (n=20)	Patients with atypical symptoms (n=6)
Once-daily, n (%)	11 (42)	9 (45)	2 (33)
Twice-daily, n (%)	15 (58)	11 (55)	4 (66)

PPI Proton pump inhibitor

TABLE 3
Distribution of patients with abnormal pH test results based on criterion 2 in Table 1 (n=26)

Patients	Total time (%) pH<4				
	5.6–8.9	9.0–12	12.1–15	15.1–25	>25
Number	7	8	4	4	3
Percentage	26.5	30.5	15	15	12

were found by Katzka et al (12), whose study included prolonged pH testing and symptom correlation scores. In those with typical GERD symptoms and abnormal pH levels on twice-daily PPI therapy, three of nine normalized their pH test and improved their clinical status with further increases in the PPI dose.

In a recent study (13) of 110 patients with gastroesophageal reflux disease or Barrett's esophagus, only 58% of patients with GERD and 52% of those with Barrett's esophagus normalized the esophageal pH on PPIs when a pH of less than 4.0 occurring less than 5.5% of the time was used as the definition of normal. When a DeMeester score of less than 14.7 was used as the definition of normal, only 44% of those with GERD normalized their scores on PPI therapy.

Our study demonstrates that in a patient population assessed by a specialist as having clinically suspected GERD that is not responding to PPI therapy, a substantial number of patients will have abnormal esophageal pH levels. Unfortunately, we did not receive clinical follow-up information for the patients in whom we identified to have abnormal esophageal acidification and, thus, we cannot be certain whether their symptoms improved following adjustment of their PPI dose or type.

The role of pH testing in the management of patients with GERD refractory to medical therapy is evolving (14). However, our data suggest that an abandonment of pH testing in these individuals would be premature. Although one limitation of the study was our relatively small database, this is not a reason to dismiss the present study's findings, because they are consistent with other published data (13).

Within specialty gastroenterology practices, 24 h pH testing in clinically refractory GERD patients identifies a substantial number of patients in whom esophageal acidification has not been normalized. Alternatives for patients who seem to be failing to respond to PPI therapy are limited. Therefore, we cannot afford to miss this subset of patients for whom increased acid suppression therapy or possibly antireflux surgery may be a treatment option.

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