

Proton pump inhibitor resistance in the treatment of laryngopharyngeal reflux

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OBJECTIVE: To describe the occurrence of relative proton pump inhibitor (PPI) drug resistance in the treatment of laryngopharyngeal reflux (LPR).

STUDY DESIGN AND SETTING: A retrospective review was performed for 1053 consecutive adults undergoing double-probe (simultaneous esophageal and pharyngeal) pH testing in our laboratory. Two hundred five patients who had pH studies performed while taking at least a daily dose of PPI therapy were identified; 167 qualified for further analysis. The pH data was reviewed for the presence of abnormalities in either esophageal or pharyngeal acid exposure to evaluate drug efficacy.

RESULTS: Forty-four percent (74/167) of the study patients demonstrated abnormal levels of acid exposure. Results were further analyzed to compare failure rates based on different dosage regimens. Patients on once daily doses of PPI failed at a rate of 56%, with lower failure rates for higher-dose regimens.

CONCLUSIONS: A significant number of LPR patients on PPI therapy demonstrate relative drug resistance. (Otolaryngol Head Neck Surg 2001;125:374-8.)

Laryngopharyngeal reflux (LPR) is a relatively common problem encountered by the otolaryngologist.

Diagnosis is often based on a history of chronic throat irritation, globus sensation, chronic cough, or chronic hoarseness combined with findings of laryngeal edema or erythema.^{1,2} Oftentimes, clinicians rely on an empirical trial of medications to establish a diagnosis. The gold standard for diagnosis, however, has remained 24-hour ambulatory double-probe pH testing. This test allows accurate detection of the presence of acid in the pharynx and therefore is a direct measure of LPR.

The treatment for LPR currently consists of dietary and lifestyle modification along with proton pump inhibitor (PPI) therapy. Results from treatment with PPIs have generally been excellent; improvement has been measured both in eradication of symptoms and improvement in laryngeal findings.² Unfortunately, not all patients respond as expected to PPIs. Some patients require higher doses of medication, a change in their PPI, or antireflux surgery to control LPR. This report reviews our experience with the treatment of LPR with PPIs, and defines the relative failure rate of this class of medication in treating this problem.

MATERIALS AND METHODS

A database review was initiated to identify all patients who have undergone ambulatory double-probe (simultaneous esophageal and pharyngeal) pH testing at The Center for Voice Disorders of Wake Forest University over a 44-month period. The technique of double-probe pH testing has been described elsewhere³ and will not be repeated here.

The records were then reviewed to identify those patients who had undergone pH testing while on PPI therapy. These tests represent drug efficacy studies. At the time of testing, patients were specifically asked about compliance with the medical regimen. Specific notations were made if the patient had been noncompliant, especially within the week before testing.

Charts of study patients were then reviewed to gather routine demographics, drug and dosage information, and test results. Calculation of relative drug resistance was based on the number of patients demonstrating abnormal pH study results despite being on PPI drug therapy. A study was judged to be abnormal if normal values were exceeded in any category listed in Table 1. Calculation of complete acid suppression was based on the number of patients with no evidence of acid

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Table 1. Criteria for failure for ambulatory double-probe pH monitoring*

% time pH < 4 upright (normal ≤ 8.1%)
% time pH < 4 supine (normal ≤ 2.9%)
% time pH < 4 total (normal ≤ 5.5%)
Total number of esophageal episodes (normal ≤ 51)
Any pharyngeal episodes (normal = 0)

*Normals for 24-hour period established for our pH laboratory.

Table 2. Results: pH monitoring data

PPI dose	N	Abnormal pH studies (% failure rate)	Complete acid suppression (%)
1 × a day	25	14 (56%)	0 (0%)
2 × a day	95	40 (42%)	13 (14%)
3 × a day	42	18 (43%)	7 (17%)
4 × a day	5	2 (40%)	1 (20%)
Total	167	74 (44%)	21 (13%)

in the pharynx or esophagus during the entire study (ie, all the measured values were zero).

RESULTS

A total of 1053 patients underwent ambulatory double-probe pH monitoring at our institution between May 1996 and January 2000. Twenty percent (205/1053) of patients were identified as having undergone studies to evaluate drug efficacy. Thirty-eight studies were excluded from the analysis; 21 because pH data were incomplete, 4 because of incomplete information on drug dosage, and 13 because patients were taking other medications that are used to treat reflux in addition to the PPI. Of the remaining 167 patients, 44% (73/167) were men and 56% were women. The average age of the patients was 49.33 years, with a range from 14 to 83 (SD = 14.259). Most of our patients were given omeprazole, with the remainder given lansoprazole. The PPI dosage schedules of the study patients are shown in Fig 1.

Data analysis showed that 31% (51/167) of patients demonstrated abnormal episodes of reflux (pH < 4) into the pharynx, and 27% (45/167) of patients had abnormal reflux into the esophagus only despite taking PPIs. In total, 74 patients had either abnormal pharyngeal or esophageal reflux, indicating that 44% of the patients had documented PPI drug resistance. When evaluated more specifically for failure rates based on drug dosage, although the trend was for improved pH study results on increased PPI dosage, the differences between dosages did not achieve statistical significance ($P = 0.638$). These results are shown in Table 2.

Table 2 also demonstrates the rates of complete acid suppression of various dosages of PPI as defined above.

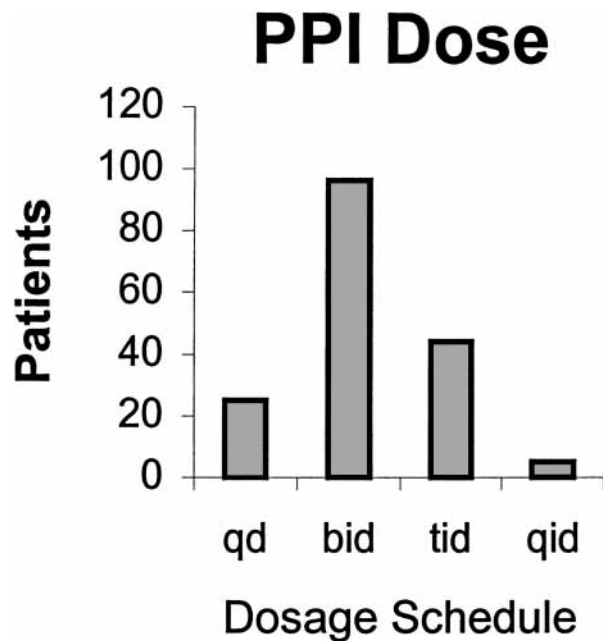


Fig 1. Bar graph represents the number of patients in the study taking various doses of proton pump inhibitor.

When comparing a once-daily dose of PPI with higher doses, there was a significant improvement in the ability of the higher doses to achieve complete acid suppression compared with once-daily dosing ($P < 0.05$).

DISCUSSION

Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR) are relatively common problems. It is estimated that between 25% and 35% of the population will experience GERD during their lifetime.⁴ Although there are no published figures as to the prevalence of LPR in the general population, we have estimated in a recent review that half of all patients presenting with a voice or swallowing complaint exhibit this problem.⁵

The treatment of acid-related disorders has evolved over time, often reflecting the development of newer medications. Initial treatment regimens relied on dietary changes and the administration of antacids. Such regimens were mostly effective in treating only mild LPR and GERD.⁶⁻⁹

With the advent of H₂ receptor antagonists, the results of treatment improved. Studies demonstrate that about 50% of patients improve with this medical regimen, leaving a significant proportion of patients without benefit.^{4,10} This is largely due to the inability of H₂ blockers to inhibit meal-stimulated acid secretion. In addition, with continued usage of H₂ blockers, it was found that many patients eventually developed a toler-

ance to the drugs, limiting the long-term effectiveness of these medications.^{11,12}

In the 1980s, a new class of drugs was introduced in the United States—proton pump inhibitors. These drugs acted by directly inhibiting H⁺-K⁺ ATPase, a key enzyme in the final acid production pathway within the stomach parietal cell. The elimination or marked suppression of acid production accomplished 2 things: it reduced exposure of damaged tissues to an acidic environment, and more importantly, it reduced the activity of pepsin, which requires an acidic pH to function.

In general, PPIs have been remarkably effective in treating patients with LPR. Clinical trials have confirmed their superiority to H₂ blockers both in symptom relief and in mucosal healing.^{13,14} Theoretically, this is because PPIs act at the final common pathway of acid production, as opposed to H₂ blockers, which modulate acid output through blocking stimulation of the parietal cell. Because of this, PPIs have the ability to more completely suppress acid production (basal and meal stimulated).

Despite this, there remains a group of patients whose treatment fail with standard doses of these medications. These patients either require higher than usual doses of medication or surgical therapy to eliminate their reflux; such patients can be said to have a relative resistance to standard PPI therapy.

Few published articles have investigated PPI resistance. Klinkenberg-Knol and Meuwissen¹⁵ discussed the finding of PPI treatment failures in 19 patients with GERD who had also experienced treatment failure on high dose H₂ blockers. Most of these patients had severe disease and experienced complications related to GERD. The authors recommended the use of pH testing to adjust dosing in such patients. Leite et al¹⁶ studied 88 patients given twice daily doses of omeprazole, and found that 19% represented treatment failures when studying gastric and distal esophageal pH exposure. To our knowledge, there is only a single article discussing relative PPI resistance in the treatment of LPR. Bough et al¹⁷ studied 6 patients whose treatment had clinically failed with a twice-daily dosage of omeprazole for LPR. Results demonstrated that all the patients continued to have significant acid production, as measured by pH testing. However, the applicability of the results to the treatment of LPR is questionable, as the proximal probe was placed in the lower esophagus during testing, and this probe configuration does not document LPR.

Although it is clear that many patients have incomplete acid suppression on PPI therapy, it is not known why this occurs. Theoretically, patients on twice-daily doses of PPI should have near-complete 24-hour acid

suppression. Incomplete suppression may suggest a shorter duration of drug action in these patients, possibly through increased metabolism of the PPI by the liver.

A recent trial¹⁸ demonstrated that a majority of patients and controls taking PPIs had nocturnal acid breakthrough leading to drops in intragastric pH to below 4 for a significant period of time. This study demonstrated that breakthrough occurs at an average of 7.5 hours after the evening dose. This is significantly worse than a previous study¹⁹ that demonstrated breakthrough at 13.8 hours after the morning dose. The authors of the recent study¹⁸ conjectured that the reason for this decreased activity time was possibly due to 2 factors: the lack of buffering effect from food in the stomach at night, and the poorer ability of PPIs to bind inactive proton pumps (proton pumps are more active during the day, when they are repeatedly stimulated by food).

Another explanation for poor response to medical therapy is poor bioavailability of the drug. Ashida et al²⁰ demonstrated that 9 of 10 patients with resistant gastric ulcers had decreased plasma levels of PPI when compared with controls. They suggested that this was due to an increase in gastric emptying time. In our series, we did not measure gastric emptying time.

Leite et al¹⁶ hypothesized that patients that failed standard twice daily doses of PPIs might have gastric hypersecretion in response to meals. This was suggested by their finding that patients whose omeprazole therapy was failing demonstrated a lack of meal buffering effect compared with normal controls. It is notable that basal acid output was normal in these patients.¹⁶

Tolerance to the drug may be another mechanism of treatment failure. Although there is no current evidence to demonstrate that patients may become tolerant to PPIs, there is evidence that shows that tolerance does develop to H₂ blockers. Anecdotally, we have found that patients taking one type of PPI often demonstrate improvement when switched to an equivalent dosage of another PPI.

A final explanation for drug failure is poor patient compliance. PPIs are currently quite expensive, and this compounds the problem of patients skipping doses. In this study, patients were questioned specifically to insure compliance before testing.

Whatever the reason, relative PPI resistance is an important problem in treating patients with reflux disease. Drug resistance encountered during a trial of empiric therapy would result in an incorrect diagnosis. In established LPR and GERD patients, suboptimal dosing may result in the progression of reflux-related disorders and months to years of wasted money on inef-

fective medical therapy. In patients who have recently undergone vocal fold surgery, the inability to totally suppress acid may result in vocal fold scarring, the progression of airway stenosis, and other complications associated with LPR. For these reasons, we use drug efficacy tests regularly on patients who do not improve on standard dose PPI therapy, yet have strong clinical evidence of reflux.

This series reviews a large cohort of patients diagnosed with LPR who had undergone ambulatory dual-probe pH monitoring while on PPI therapy. The results point to a relatively high rate of failure of PPIs to control acid reflux. It is particularly interesting to note that once-daily dosing of PPIs resulted in a greater than 50% failure rate in our patient group; this is often the starting dose that is used in many institutions and is recommended by the manufacturers of these drugs. It is important to note that the incidence of PPI drug failures in this study may be overestimated, because the patients having drug efficacy studies were selected on the basis of their poor clinical response to LPR therapy. When compared with the results found in the study by Leite et al,¹⁶ the rate of PPI failure in the current study was much higher (42% vs 19% for twice a day therapy). On closer inspection, however, when our results are analyzed specifically for esophageal reflux (leaving out patients with pharyngeal reflux), the failure rate was lower (27%), more consistent with the previous work. Further randomized studies including controls would be necessary to give a true estimate of the efficacy of this class of drugs for both GERD and LPR.

The data of this study must be interpreted within the context of the broader population of patients with LPR. Clearly, this is a select group of patients, and the overall treatment failure rate in the general population is likely to be lower. It is difficult to extrapolate the true number from our data, as there are inherent selection biases involved in this type of retrospective analysis.

In analyzing the results of the study, we found several important issues. Although we were able to demonstrate a significant improvement in the ability of higher doses of PPI to achieve complete acid suppression, higher doses in this study did not result in an improvement in pH study failure rate. Such an improvement has been shown in previous studies. Kuo and Castell²¹ found improved gastric acid suppression with twice daily dosing of 20 mg of omeprazole when compared with once daily dosing of 40 mg. Harder et al²² studied different dose schedules of lansoprazole, and found that there was an advantage of twice daily dosing of 15 mg lansoprazole over once daily dosing of 30 mg with respect to nocturnal pH values. We suspect that the lack of such a finding in our study is due to the same patient selection issues noted above.

In our practice, we continue to use high dose PPI therapy in patients suspected of having significant LPR. In certain instances, our goal is to achieve complete acid suppression. Complete acid suppression may be vital in several clinical situations: subglottic stenosis, granulomas, leukoplakia, and laryngospasm. In patients with these problems, even minimal pharyngeal acid exposure may lead to lack of improvement or progression of disease. Our data show that complete acid suppression is quite difficult to achieve with medical therapy. Patients with the aforementioned conditions or other reflux-associated conditions that have incomplete acid suppression on drug efficacy studies may benefit from early consideration for fundoplication.

CONCLUSIONS

Proton pump inhibitors as a class of drugs are generally effective in treating patients with LPR and GERD. Despite their ability to act on the final common pathway of acid production, they are not completely effective in suppressing acid in all patients. This is particularly significant in LPR patients, since the laryngeal and pharyngeal mucosa is particularly sensitive to acid and pepsin exposure. Until now, there has been no study regarding the efficacy of PPIs in eliminating acid exposure in this group of patients. Our data indicate that relative resistance to PPIs is more common than previously suspected.

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