Effect of Aggressive Therapy on Laryngeal Symptoms and Voice Characteristics in Patients with Gastroesophageal Reflux

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Gastroesophageal reflux (GER) is associated with a variety of laryngopharyngeal signs and symptoms. Injury of the laryngopharynx as a result of GER can be refractory to conventional antireflux therapy. This prospective study was undertaken to evaluate the prevalence of laryngopharyngeal signs and symptoms in patients with documented GER and to assess the response to a high-dose combination antireflux therapy consisting of cisapride and pantoprazole. Twenty-two patients with symptoms of GER were enrolled. After baseline evaluation using a history questionnaire for symptoms, laryngeal endoscopy and vocal acoustic analysis, patients were started on treatment consisting of pantoprazole 40 mg b.d. and cisapride 20 mg twice daily. Repeat history and otolaryngologic evaluation was performed at 4 weeks. Laryngopharyngeal symptoms were frequent in most patients, with throat clearing and globus being the most prevalent symptoms followed by vocal fatigue and excess mucus production. Almost 90% of the patients had abnormal endoscopic laryngeal findings but the acoustic parameters did not show any abnormal results except for mild elevation in the shimmer. After treatment, all symptoms and endoscopic abnormalities improved significantly except for intermittent dysphonia and laryngeal mucosal redness. Acoustic abnormalities did not change significantly following therapy. Laryngeal symptoms and voice abnormalities are highly prevalent in patients with GER. Combination antireflux therapy with a proton pump inhibitor and a prokinetic agent results in rapid symptomatic and endoscopic response in the majority of patients. *Key words*: *cisapride*, *gastroesophageal reflux*, *laryngitis*, *pantoprazole*, *voice*.

INTRODUCTION

Gastroesophageal reflux (GER) is a common physiologic occurrence described as retrograde movement of gastric contents. GER can result in injury to the mucosal lining of the esophagus and in some cases the laryngopharynx, which is not adapted to the presence of potentially noxious materials such as acid, pepsin and pancreatic enzymes. As such, GER has been implicated in the pathogenesis of a host of upper airway diseases, including stridor, recurrent croup, subglottic stenosis, laryngospasm, chronic cough and obstructive apnea (1–3). Lower airway manifestations of reflux, including asthma, bronchitis, bronchiolitis and recurrent pneumonia, have also been described (4, 5).

Using single- and dual-probe 24-h ambulatory pH monitoring, Koufman (6) studied the otolaryngologic manifestations of GER in 225 patients, thereby directly supporting the associations mentioned above. Other studies have corroborated these findings and the notable benefit of antireflux therapy has provided indirect but additional convincing evidence of the association between GER and some laryngeal disorders (7–9). Despite considerable advances in understanding the role of GER in laryngeal disorders, the exact prevalence of laryngeal signs and symptoms in patients with GER remains largely unknown. The incidence of posterior laryngitis and its association with reflux is still debatable. Furthermore, in patients with atypical manifestations of GER, the choice of medical therapy, dosage and duration of treatment is not clearly established. Studies have looked primarily at the efficacy of proton pump inhibitors (PPIs), such as omeprazole and lansoprazole, in patients with GER-associated laryngitis and have shown a significant, albeit slow, response in laryngeal signs and symptoms, with a mean response time of 8 weeks (10). This slow, and at times incomplete, response may be due to occasional breakthrough of acid control, particularly nocturnal breakthrough, a well-described phenomenon that may be preventable by the addition of the prokinetic agent cisapride or nocturnal H_2-receptor antagonists (11, 12). Because of the extreme sensitivity of the laryngopharynx to any acid in the refluxate, sustained acid control as well as diminution of reflux contact time in the hypolarynx are both necessary.

This study is designed to evaluate two issues of debate: (i) the prevalence of laryngeal signs and symptoms in patients with known GER and their corresponding acoustic evaluation; and (ii) the role of combination antireflux therapy using high-dose pantoprazole, a PPI, in combination with the prokinetic agent cisapride. Clinical symptoms, laryngeal endoscopic findings and acoustic analyses of patients were obtained at baseline and after completing the 4-week regimen. Whether the proven potentiated and en-

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hanced response of a combined antireflux treatment in the gastrointestinal tract is also seen in the upper airway is discussed. To our knowledge, this is the first study to evaluate the efficacy of this short-term combination therapy on prevalent laryngeal signs and symptoms in patients with GER and to associate it with the vocal acoustic analysis of these patients.

MATERIALS AND METHODS

A total of 22 patients with typical complaints of GER were prospectively studied. Patients were thoroughly evaluated by a gastroenterologist and an otolaryngolgist prior to their enrollment in the study. Patients with a history of daily heartburns, regurgitation or oral water brash or patients diagnosed to have GER by endoscopic evidence of esophagitis or by 24-h pH monitoring were included in this study. Patients already on antireflux treatment at the time of their examination were excluded. Patients diagnosed to have malignant laryngeal lesions by laryngeal endoscopy were also excluded. Informed consent was obtained prior to treatment. Nocturnal antireflux precautions were given, including avoiding eating or drinking for 3 h prior to bed time and elevation of the head of the bed by $\approx$ 30° during sleep. Patients were started on pantoprazole 40 mg b.d. and cisapride 20 mg b.d., administered half an hour before meals. None of the patients had any contraindications to the use of cisapride, including history of heart or kidney disease, family history of sudden death or concomitant use of diuretics, antihistamines, azole or macrolide antimicrobials.

Patients were evaluated at baseline and after 4 weeks of antireflux treatment. The evaluation included a history questionnaire, laryngeal endoscopic examination and vocal acoustic analysis. The history questionnaire consisted of a list of questions about upper airway symptoms commonly seen in patients with reflux. The list included chronic or intermittent dysphonia, vocal breaks or fatigue, throat cleaning or excess mucus, chronic cough, odynophonia and globus pharyngeus. The laryngeal endoscopic evaluation aimed at assessing the degree of posterior laryngeal inflammation using a 70° Hopkins rigid scope attached to a 30 mm single-chip color endoscopic video camera. The laryngeal inflammation at the posterior commissure was photographed and categorized as opalescent red mucosa over the arytenoids or edema of the posterior commissure with absence of the normal concavity. The acoustic analysis was performed by recording the vocal signal directly into the VISI pitch system model 3300 using a condenser microphone at a distance of 15 cm from the mouth. Two modules were used: the vocal quality assessment and pitch energy display modules. Examined parameters included the fundamental frequency (F0), habitual pitch, pitch range, relative average perturbation (RAP), voice energy, shimmer, noise-to-harmonic ratio (NHR), voice turbulence index (VTI) and maximum phonation time. The F0, RAP, shimmer, VTI and NHR were recorded by asking the patient to sustain the vowel sound "ah" for 2 s. The maximum phonation time was recorded by asking the patient to take a deep breath and sustain phonation for as long as possible. The habitual pitch was recorded by asking the patient to count to 10. Cochran's Q test was used for statistical analysis of symptoms and endoscopic findings. The paired t-test was used for statistical analysis of the acoustic variables.

RESULTS

The most prevalent symptoms were throat clearing (72.7%) and globus (63.6%), followed by vocal fatigue (59.1%) and excess mucus (59.1%). A history of intermittent dysphonia was present in almost 50% of cases and one-quarter had chronic dysphonia at the time of presentation. Almost 90% of the patients enrolled in the study had abnormal endoscopic laryngeal findings, ranging from redness (40.9%) to edema of the posterior commissure (50%). The acoustic parameters did not show any abnormal results except for possible mild elevation in the shimmer, defined as cycle-to-cycle variation in amplitude (4.87 dB in males and 5.47 dB in females) (Table I). Following treatment, all symptoms improved statistically ($p < 0.05$) except for intermittent dysphonia ($p = 0.083$) and chronic cough and odynophonia (Fig. 1). Chronic cough and odynophonia were excluded from the statistical analysis in view of the low prevalence of these symptoms in the study patients (one and three patients, respectively).

Table I. *Average baseline acoustic values distributed by gender. There were no significant changes in any of the parameters listed after treatment*

Acoustic variable	Males	Females
Average fundamental frequency (Hz)	133.74	204.49
Relative average perturbation (%)	0.94	1.43
Shimmer (%)	4.87	5.47
Noise:harmonic ratio	0.15	0.14
Voice turbulence index	0.04	0.07
Habitual pitch (Hz)	124.74	190.86
Pitch range (Hz)	123.08	196.61
Maximum phonation time (sec)	17.07	7.18
Voice energy (dB)	63.32	62.19

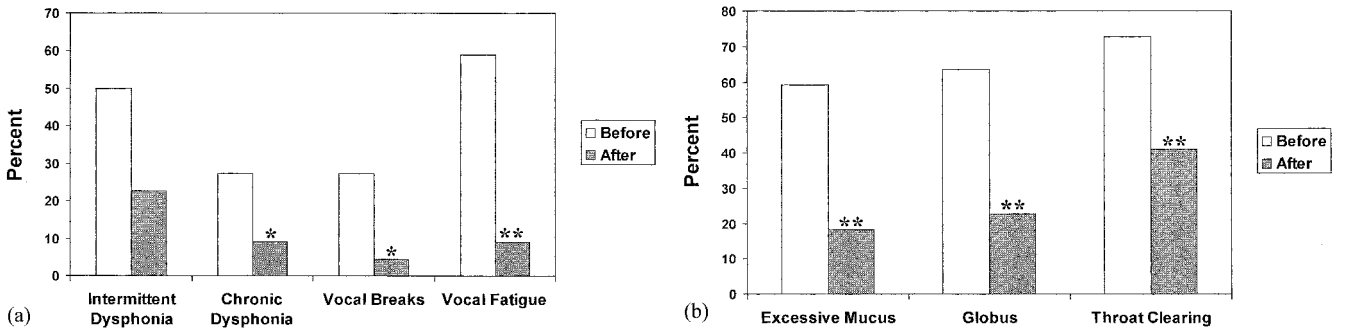

Fig. 1. Prevalence of symptoms before (open bars) and after (filled bars) treatment. *$p < 0.05$; **$p < 0.01$ when compared to baseline.

In terms of the endoscopic findings, laryngeal edema at the posterior commissure showed a significant change after treatment ($p < 0.001$). However, there was no statistically significant change in the laryngeal mucosal redness. Acoustic analysis showed no statistically significant changes in any of the parameters before and after treatment (Table I).

DISCUSSION

The association between GER and laryngeal diseases has only been reported in the last two decades, sparking a wave of change in the practice of otolaryngology. It is estimated that 4–10% of patients presenting to an otolaryngology practice will have symptoms and/or findings related to GER (2). Two hypotheses have emerged in an attempt to explain this relationship: one based on direct mechanical injury to the mucosal lining by the acid–pepsin reflux; and the other on a vagally-mediated response in the distal esophagus that triggers throat clearing and irritation, with resultant laryngeal pathology formation (13–16).

GER may present either as typical heartburn and regurgitation, as commonly seen in the gastroenterology clinic, or atypically as ill-defined laryngopharyngeal and cervical symptoms often seen by otolaryngologists. Moreover, the prevalence of laryngopharyngeal symptoms (i.e. dysphonia, cough, hoarseness, globus, vocal fatigue, throat clearing and excessive mucus) related to GER in patients with typical symptoms (heartburn and regurgitation) at presentation varies between studies, primarily because these atypical manifestations may be underdiagnosed in patients seen in gastroenterology practices.

Even though it has been estimated that almost half of all otolaryngology patients complaining of vocal problems have GER as a significant co-factor, its undisputed etiological role remains controversial. This has been attributed to variations in the endoscopic laryngeal findings, lack of symptoms such as heartburn or regurgitation, lack of sensitivity and specificity of traditional diagnostic tests of GER, such as barium esophagogram and endoscopy, and failure of rapid response to conventional antireflux therapy in many cases. In our study, $\approx$ 50% of patients had a history of intermittent dysphonia associated with reflux and 27.3% had dysphonia at the time of presentation but only 4.5% had cough. Patients with chronic dysphonia improved after treatment ($p < 0.05$) but those with a history of intermittent dysphonia did not show a statistically significant improvement, suggesting that a longer period of treatment may be needed. Vocal fatigue and vocal breaks were prevalent in our patients (59% and 27%, respectively) and improved significantly with therapy.

The association of posterior laryngitis with GER is being increasingly accepted. Ohman et al. (17) showed that 75% of patients with previous or present contact laryngeal ulcers had abnormal reflux studies, while Hanson et al. (18) noted that 96% of patients with chronic laryngitis responded to antireflux therapy. In our study of patients presenting to a gastroenterology practice, endoscopic abnormalities were prevalent. Opalescent redness over the posterior commissure was noted in $\approx$ 40% of patients while 50% had posterior laryngeal edema. The effect of therapy on redness was not statistically significant ($p = 0.3$) but was highly significant for laryngeal edema ($p < 0.001$). This may imply that the mucosal redness often observed in the posterior commissure may be a normal or non-specific finding, whereas mucosal edema has more of a cause-to-effect relationship to reflux.

The use of potent acid-suppressive agents such as PPIs has proven to be highly successful in the rapid control of symptoms and in the healing of the esophageal signs and symptoms in patients with severe GER. Even when used once daily, these agents can achieve these desirable effects in the majority of these patients. In contrast, most patients with reflux-

associated laryngitis fail to respond completely to single-dose PPIs and have frustratingly slow rates of symptomatic response and laryngeal healing despite high-dose therapy (2, 10). How can one reconcile these differences between the esophagus and larynx? Peghini et al. (11) showed that nocturnal acid breakthrough (arbitrarily defined as intragastric pH < 4 for > 1 h overnight) occurred in 73% of patients with GER as well as in normal volunteers taking 20 mg of omeprazole daily. This percentage was reduced only from 48% to 31% with an additional bedtime dose of omeprazole but to as low as 5% with 150 mg of ranitidine at bedtime. Similarly, in patients with GER treated twice daily with omeprazole, the addition of the prokinetic agent cisapride at bedtime resulted in a substantial reduction in nocturnal acid contact time in the esophagus as measured with 24-h pH monitoring (12). Based on the above findings, it appears that the doses of PPIs used effectively for reflux esophagitis may not prevent nocturnal acid breakthrough (which is especially injurious because of delayed clearance at night) (19). This issue may be of great importance as it pertains to the laryngopharynx which, unlike the esophagus, is exquisitely sensitive to even minute but repeated amounts of acid refluxate.

Our study shows that in a cohort of patients with typical GER presenting to a gastroenterologist, laryngeal symptoms and laryngoscopic findings are prevalent, ranging from minor to severe laryngitis. Furthermore, our results show that the use of cisapride in addition to twice daily pantoprazole results in rapid improvement in most prevalent laryngeal symptoms and signs. To our knowledge, this is the first study to report on the efficacy and rapid response to this combination therapy.

The lack of change in the acoustic analyses is likely due to the fact that our patients did not present because of laryngeal symptoms (only 27.3% of our patients had dysphonia and the rest had either a history of intermittent dysphonia noted with the reflux episodes or no noticeable change in voice quality). In the group of patients who had dysphonia and improved on treatment, the absence of acoustic correlation can be attributed to two things: (i) the laryngeal findings, ranging from edema to redness, were in practice limited to the posterior commissure, and hence the vibratory part of the vocal folds was not involved; and/or (ii) as acoustic analysis is limited to periodic sounds, severe dysphonia at the time of examination may cause a decrease in periodic:aperiodic sound ratio, resulting in lower accuracy and reliability of the test.

CONCLUSION

Our study shows that laryngopharyngeal symptoms are very common in patients with typical GER. Awareness of this association is a prerequisite for successful management of these symptoms. Short-term (4-week) aggressive treatment with a high-dose PPI in combination with a prokinetic agent appears to be beneficial but a large placebo-controlled randomized trial is needed to clearly address this issue. Relapse is probably high once therapy has terminated and the role or choice of maintenance therapy is unclear.

REFERENCES

1. Bain WM, Harrington JW, Thomas LE, Schaefer SD. Head and neck manifestations of gastroesophageal reflux. Laryngoscope 1983; 93: 175–9.
2. Ormseth EJ, Wong RK. Reflux laryngitis: pathophysiology, diagnosis, and management. Am J Gastroenterol 1999; 94: 2812–7.
3. Little FB, Koufman JA, Kohut RI, Marshall RB. Effect of gastric acid on the pathogenesis of subglottic stenosis. Ann Otol Rhinol Laryngol 1985; 94: 516–9.
4. Burton DM, Pransky SM, Katz RM, Kearns DB, Seid AB. Pediatric airway manifestations of gastroesophageal reflux. Ann Otol Rhinol Laryngol 1992; 101: 742–9.
5. Kelly K, Latimer J, Johnson L. Dual pH probes for the evaluation of gastroesophageal reflux in pediatric patients with chronic pulmonary symptoms [Abstract]. Gastroenterology 1986; 90: 1489.
6. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope 1991; 101: 1–78.
7. Little JP, Matthews BL, Glock MS, et al. Extraesophageal pediatric reflux: 24-hour double-probe pH monitoring of 222 children. Ann Otol Rhinol Laryngol Suppl 1997; 169: 1–16.
8. Wilson JA, White A, von Haacke NP, et al. Gastroesophageal reflux and posterior laryngitis. Ann Otol Rhinol Laryngol 1989; 98: 405–10.
9. Wo JM, Grist WJ, Gussack G, Delgaudio JM, Waring JP. Empiric trial of high-dose omeprazole in patients with posterior laryngitis: a prospective study. Am J Gastroenterol 1997; 92: 2160–5.
10. Shaw GY, Searl JP. Laryngeal manifestations of gastroesophageal reflux before and after treatment with omeprazole. South Med J 1997; 90: 1115–22.
11. Peghini PL, Katz PO, Castell DO. Ranitidine controls nocturnal gastric acid breakthrough on omeprazole: a controlled study in normal subjects. Gastroenterology 1998; 115: 1335–9.
12. Inauen W, Emde C, Weber B, et al. Effects of ranitidine and cisapride on acid reflux and oesophageal motility in patients with reflux oesophagitis: a 24 hour ambulatory combined pH and manometry study. Gut 1993; 34: 1025–31.

13. Johnson LF, Harmon JW. Experimental esophagitis in a rabbit model. Clinical relevance. J Clin Gastroenterol 1986; 8 (Suppl 1): 26–44.
14. Lillemoe KD, Johnson LF, Harmon JW. Role of the components of the gastroduodenal contents in experimental acid esophagitis. Surgery 1982; 92: 276–84.
15. Ward PH, Berci G. Observations on the pathogenesis of chronic non-specific pharyngitis and laryngitis. Laryngoscope 1982; 92: 1377–82.
16. Ward PH, Zwitman D, Hanson D, Berci G. Contact ulcers and granulomas of the larynx: new insights into their etiology as a basis for more rational treatment. Otolaryngol Head Neck Surg 1980; 88: 262–9.
17. Ohman L, Olofsson J, Tibbling L, Ericsson G. Esophageal dysfunction in patients with contact ulcer of the larynx. Ann Otol Rhinol Laryngol 1983; 92: 228–30.
18. Hanson DG, Kamel PL, Kahrilas PJ. Outcomes of antireflux therapy for the treatment of chronic laryngitis. Ann Otol Rhinol Laryngol 1995; 104: 550–5.
19. Hatlebakk JG, Katz PO, Kuo B, Castell DO. Nocturnal gastric acidity and acid breakthrough on different regimens of omeprazole 40 mg daily. Aliment Pharmacol Ther 1998; 12: 1235–40.

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