Results of empiric therapy with proton-pump inhibitor in patients with voice disorders

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ABSTRACT

The aim of this experiment was to analyze the results of routine therapy with proton-pump inhibitor (PPI, omeprazole) in patients who were referred to phoniatric outpatient clinic with laryngeal changes of suspected laryngopharyngeal reflux (LPR) etiology. The study included forty (40) patients with pharyngeal and laryngeal problems co-existing with laryngoscopic findings typical for LPR. All patients were qualified for 6-weeks therapy with omeprazole (20 mg once a day, 30 to 45 min before meal), along with topical solution for pharyngeal gargling. Laryngovideostroboscopy, analysis of the vocal fold oscillations (NAPZ scale), determination of maximal phonation time (MPT), and perceptual voice analysis (GRBAS scale) were performed prior to and after six weeks of the therapy. Following the therapy, all patients showed at least 7-point improvement in the reflux score index, and at least 2-point improvement of the reflux finding score was documented in 82.5% of the subjects. The therapy was reflected by significant improvement of A, P, and Z parameters of GRBAS scale. At a baseline, 24 patients (60%) had an incomplete phonatory closure; this prevalence was reduced to 17 cases (42.5%) following the IPP therapy. Six weeks therapy with omeprazole attenuates phoniatric symptoms of LPR and improves laryngeal morphology and function. Therapeutic response to empiric administration of IPP constitutes the important diagnostic criterion of LPR.

Key words: Laryngopharyngeal reflux, laryngovideostroboscopy, omeprazole, reflux finding score, reflux symptom index.

INTRODUCTION

Reflux laryngitis and/or pharyngitis and related voice disorders constitute frequent reasons of referral to phoniatrcian or laryngologist. Due to non-specific character of symptoms reported by most patients, proper diagnosis of laryngopharyngeal reflux (LPR) should be based on the detailed analysis of personal history and modern diagnostic imaging; the latter is also helpful during the monitoring of treatment outcomes. LPR-associated symptoms are reported by 15 to 20% of population and are responsible for nearly 15% of referrals to laryngology outpatient clinics (Qadeer et al., 2005; Vaezi, 2008). These symptoms are observed in about 50% of patients with voice disorders (Ormseth and Wong, 1999) and the frequency of co-incidence of pathological gastroesophageal reflux (GERD) and reflux laryngitis is estimated at 18 to 75% (Ylitalo et al., 2001). However, confirming causative relationship between GERD and changes present in the upper airways requires resolution of the latter following empiric therapy with double or triple dose of proton-pump inhibitor (PPI), continued for 1 to 3 months and accompanied by proper lifestyle modification (Chandra and Harding, 2007; Kahrilas, 2008; Modlin et al., 2009). In addition, the monitoring of airway pH (for example, using Dx-pH
measurement system) can be helpful in confirming the relationship of LPR with pharyngeal and laryngeal changes (Golub et al., 2009; Wiener et al., 2009).

LPR-specific changes include the hypertrophy of the posterior commissure, subepiglottic edema, hyperemia and/or edema of the vocal folds, diffused laryngeal edema and presence of granulation tissue in the larynx and intralaryngeal retention of thick mucus. According to Belafsky et al. (2001), diagnosis of laryngopharyngeal reflux and prognosis of positive response to PPI therapy are suggested by more than 13 points of the Reflux Symptom Index (RSI) and the Reflux Finding Score (RFS) higher than 7 points. However, there is a considerable fraction of asymptomatic individuals who meet the aforementioned criteria which points to low specificity and low positive predictive value of RSI and RFS diagnostic systems, and suggest the lack of correlation between the presence and intensity of clinical symptoms and laryngoscopic evidence of changes. Moreover, inconsistency between consecutive laryngeal examinations performed by the same and different examiners was reported (Qadeer et al., 2005; Park et al., 2005). This can result in the over-diagnosis of LPR (Kendall, 2006).

The role of empiric therapy is not limited to the management of various disorders (for example, empiric antibiotic therapy of extra-hospital pneumonia); it can also be useful in the diagnosis of several conditions (as so-called therapy as investigation) since the effectiveness of an agent prescribed to attenuate the symptoms can confirm the presence of the underlying disease. This latter situation pertains to the diagnosis of febrile states of unknown etiology (for example, empiric antibiotic therapy) or conditions associated with excessive secretion of hydrochloric acid (for example, empiric therapy with PPIs), among others.

The aim of this study was to analyze the results of routine therapy with PPI (omeprazole) in patients referred to phoniatric outpatient clinic with laryngeal changes of suspected LPR etiology. We verified if diagnostic modalities available at phoniatric clinic were sufficient for the implementation of empiric IPP therapy in patients with voice disorders associated with LPR symptoms. Moreover, we analyzed whether PPI therapy proved effective in this indication.

All the procedures were approved by the Local Ethics Committee of the Ludwik Rydygier Collegium Medicum in Bydgoszcz. The subjects gave their informed consent before the start of any procedure.

Reflux Symptom Index (RSI) was calculated for each patient based on the questionnaire proposed by Belafsky et al. (2001). This questionnaire grades the intensity of nine symptoms using 0 to 5 point scale. Moreover, all participants were subjected to laryngovideostroboscopic examination, with the reflux finding score (RFS) determined based on eight laryngovideostroboscopic parameters graded in 0 to 4 scale (Belafsky et al., 2001). Furthermore, the following characteristics of the vocal fold oscillations were determined qualitatively using the NAPZ scale: N - symmetry and regularity of oscillation (1 - symmetric and regular, 2 - asymmetric and irregular), A - oscillation amplitude (1 - normal, 2 - reduced or prolonged), P - mucosal wave (1 - normal, 2 - limited, 3 - lack of the shift), and Z - phonatory closure (1 - complete, 2 - incomplete) (Wiskirska-Woźnica, 2002). Additionally, the consecutive phases of glottal closure and opening were examined during the stroboscopic evaluation. Kymographic recordings were analyzed using the DiagNoScope Specialista software (DiagNova). The maximal phonation time (MPT) was determined as a mean value of two consecutive measurements and a perceptual voice analysis performed using the GRBAS scale. In this scale, four grades of hoarseness are distinguished: G0 - normal voice, G1 - mild hoarseness, G2 - moderate hoarseness, and G3 - severe hoarseness. The remaining voice parameters were examined similarly: 1) roughness (R), 2) breathiness (B), 3) asthenicity (A), and strain (S).

All patients qualified for this study were prescribed six weeks therapy with omeprazole (20 mg once a day, 30 to 45 min before meal), along with topical solution for pharyngeal gargling (glycerin, vitamin E, vitamin A+D3). Additionally, physiotherapy was ordered in cases of the glottic insufficiency. Moreover, all patients were recommended to reduce body weight, have frequent, small meals, avoid or minimize consumption of reflux producing foods (fat and preserved meals, fizzy drinks) and eating late and elevate the bed’s head by 15 cm.

The complete phoniatric examination was repeated after six weeks of the IPP therapy. The laryngological and phoniatric criteria of improvement included a decrease in RSI and RFS, by at least seven and at least two points, respectively. The normal distribution of the continuous variables was tested using the Kolmogorov-Smirnov test. The statistical significance of treatment related changes was tested with the Wilcoxon signed-rank test and the McNemar’s test. The power and direction of RFS’s relationship with GRBAS and NAPZ scores were analyzed based on the Spearman’s rank coefficients ($R$). Calculations were performed using the Statistica 10 (StatSoft®, Tulsa, OK, USA) software and statistical significance was defined as $P \leq 0.05$.

**MATERIALS AND METHODS**

The study included forty (40) patients (23 women and 17 men) aged between 27 and 73 years (mean 53.7 years) referred to the phoniatric outpatient clinic due to pharyngeal and laryngeal problems. Co-existence of voice disorders with laryngoscopic findings typical for LPR was the inclusion criterion of this study. Exclusion criteria from the study were habitual smoking, occupational voice use and exposure to inhalatory medications.
Table 1: Clinical characteristics of patients suspected of LPR (n=40) determined prior to and six weeks following omeprazole therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P-value</th>
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<tbody>
<tr>
<td>RSI</td>
<td>22.2 (median 23.0; 11.0 - 35.0)</td>
<td>9.6 (10.0; 0.0-19.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RFS</td>
<td>11.9 (12.0; 6.0-23.0)</td>
<td>8.3 (8.0; 0-19.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NAPZ score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>1.12</td>
<td>1.10</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>A</td>
<td>1.75</td>
<td>1.60</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>P</td>
<td>1.20</td>
<td>1.05</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Z</td>
<td>1.57</td>
<td>1.37</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>MPT</td>
<td>13.4 (8-22)</td>
<td>15.8 (10-25)</td>
<td></td>
</tr>
<tr>
<td>GRBAS score</td>
<td>6 (4-10)</td>
<td>5 (4-10)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>G</td>
<td>1.57</td>
<td>1.30</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>R</td>
<td>1.35</td>
<td>1.10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B</td>
<td>1.02</td>
<td>1.05</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1.15</td>
<td>1.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>S</td>
<td>1.35</td>
<td>1.25</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

LPR – Laryngopharyngeal Reflux, RFS – Reflux Finding Score, RSI – Reflux Symptom Index, NAPZ scale – analysis of the vocal fold oscillations, MPT – maximal phonation time, GRBAS scale – perceptual voice analysis (Grade, Roughness, Breathiness, Asthenia, Strain).

RESULTS

Most patients (n=23, 57.5%) did not report significant gastric complaints and had no gastroenterological history. The remaining 17 individuals (42.5%) were previously treated due to alimentary problems but were not associated with current pharyngeal and laryngeal complaints.

Table 1 shows pre- and post-treatment clinical findings. Average baseline RSI was 22.2 points; this was reduced to 9.6 points on average following the IPP therapy. All patients showed at least 7-point improvement in RSI. Average pre- and post-treatment RFS was 11.6 and 8.2 points, respectively. At least 2-point improvement of RFS was documented in 82.5% of patients, but still none of them showed normal laryngeal mucosa.

Laryngovideostroboscopy revealed significant treatment-related changes in A, P, and Z parameters. Insufficiency of internal laryngeal muscles was examined with Z parameter – phonation closure. At a baseline, 24 patients (60%) had an incomplete phonatory closure; this prevalence was reduced to 17 cases (42.5%) following the IPP therapy. Prior to the therapy, the median value of maximal phonation time amounted to 13.4 s (range 8 to 22 s); this value increased to 15.8 s (10 to 25 s) following the treatment.

Both pre- and post-treatment GRBAS scores ranged from 4 to 10 points (median 6.0 and 5.0, respectively). Significant improvement was observed in the case of G, R, A, and S parameters (Table 1). Significant correlation was observed between pre- and post-treatment RFS values and the respective NAPZ scores (pre-treatment: R=0.36, P=0.02; post-treatment R=0.33, P=0.03). In contrast, RFS did not correlate significantly with GRBAS scores prior to or after the IPP therapy (pre-treatment: R=0.29, P=0.06; post-treatment R=0.303, P=0.05). None of the patients reported any side effects related to IPP therapy.

DISCUSSION

This study revealed attenuation of LPR symptoms in all patients subjected to six weeks therapy with omeprazole; additionally, more than 80% of our subjects showed improvement in RFS scores. However, we did not observe the significant association between the improvement of clinical symptoms and laryngovideostroboscopic findings.

Qadeer et al. (2005) revealed only a weak correlation between RSI and RFS values. However, in contrast to our study, they observed that the improvement of laryngovideostroboscopic findings was more pronounced than the attenuation of LPR symptoms (Qadeer et al., 2005). Perhaps, more evident improvement of RSI in our patients can be explained in terms of additional local attenuating effect of gargling solution. Irrespective of its mechanism, the attenuation of laryngopharyngeal symptoms (RSI) following administration of omeprazole, topical gargling solution and physiotherapy, along with laryngoscopic evidence of reduced inflammatory response (RFS), enabled us empiric diagnosis of LPR in at least 80% of the patients. Obviously, we assumed that all changes documented during
the six weeks follow-up resulted solely from the therapy rather than the simultaneous reduction of upper airway exposure to irritating factors other than acid gastroesophageal reflux (Vaezi, 2010). As earlier mentioned, the diagnosis of LPR is based on two important criteria with the first being the suspicion of LPR suggested by at least 13-point RSI and 7-point RFS (Belafsky et al., 2001; Hammer, 2009), while the second is clinical improvement following empiric therapy with PPIs.

Our findings are consistent with the literature data. According to most authors, an improvement after empiric PPI therapy, confirming the causal relationship of GERD with laryngeal mucosal lesions and voice dysfunction occur in 50 to 80% of patients (Qadeer et al., 2005; Klopacka et al., 2004, 2002); only Vaezi (2010) represent a different opinion. In this study and previous researches, the resolution of mucosal redness and edema, and the reduced hypertrophy of posterior commissure were the most frequent outcomes of IPP treatment (Qadeer et al., 2005; Reichel and Issing, 2008). However, these changes rarely resolve completely as confirmed by RFS analysis in our study. Although an improvement was observed in 82.5% of the participants subjected to the IPP therapy, none of the changes were completely resolved.

Apart from the diagnosis and management of LPR, our study highlighted another potential application of empiric therapy with omeprazole, namely the reversal of vocal fold dysfunction. Therapeutic response of our patients was manifested not only by lower RSI and RFS values, but also by longer phonation time and improvement of GRBAS and NAPZ parameters. The improvement was most evident in the case of voice hoarseness and roughness (G and R parameters). In contrast, no treatment-related changes of voice breathiness (B parameter) were documented. However, the breathiness is typical for severe vocal fold insufficiency, and our group lacked patients with such dysfunction.

The LPR-associated voice dysfunction can be explained by two pathological mechanisms: (1) direct irritation of vocal fold mucosa by gastric contents, and (2) laryngeal spasm occurring secondarily to the stimulation of vagal nerve endings. The inflammation of upper airways results from the imbalance between irritating factors (hydrochloric acid, pepsin and bile acids) and local protective mechanisms such as mucosal film and neutralizing effects of carbonic anhydrase (Remacle and Lawson, 2006). In patients with efficient protective mechanisms, LPR can be asymptomatic (Ozturk et al., 2006); otherwise, recurrent episodes of LPR can cause ciliary impairment and injury, retention of mucus, chronic edema and hypertrophy of laryngeal mucosa (Belafsky et al., 2001).

Laryngitis and dysfunction of laryngeal muscles, manifesting by voice hoarseness and asthenicity, constitute the most frequent extra-esophageal manifestations of GERD (Qadeer et al., 2005; Chandra and Harding, 2007; Hammer, 2009). According to literature, GERD can occur in 78% of patients with chronic hoarseness (Vaezi, 2008). Nevertheless, differential diagnosis of hoarseness should also include other factors that can irritate pharyngeal and laryngeal mucosa, alone or in concert with GERD (Qadeer et al., 2005; Vaezi, 2008; Chandra and Harding, 2007).

Therapeutic response to IPP is confirmatory of GERD diagnosis. However, other potential gastroenterological reasons of phoniatric complaints should be considered if no improvement was observed following IPP administration. These include non-acidic reflux (Patterson et al., 2009), nocturnal gastric acid breakthrough (Sato, 2006), esophagolaryngopharyngeal reflux (EPR) (Belafsky, 2008) and overproduction of gastric juice in the esophageal foci of ectopic gastric mucosa (Bajbouj et al., 2009). These conditions can be confirmed by comprehensive gastroenterological evaluation including endoscopy and esophageal impedance-pH monitoring (Bajbouj et al., 2009), even if typical dyspeptic symptoms are lacking.

Finally, LPR-like voice dysfunction can be also associated with non-gastroenterological conditions, for example, habitual smoking, allergies, inhalatory medications used in the therapy of bronchial asthma, disorders of esophageal motility, diabetes, other systemic disorders and occupational voice use (Qadeer et al., 2005; Chandra and Harding, 2007; Vaezi, 2010).

In summary, this study emphasized several clinically important issues. Firstly, our findings point to the potential influence of upper gastrointestinal tract pathologies on laryngeal morphology and function. Secondly, they suggest that clinical practitioners can use empiric therapy with IPPs as a simple and inexpensive diagnostic tool confirming potential reflux etiology of laryngeal lesions. However, the usefulness of this challenge can be limited by the high prevalence of placebo effect in LPR patients (Reichel and Issing, 2008). Additionally, benefits associated with IPP challenge should always outweigh its potential risks. Recent reports point to several adverse effects of proton-pump inhibitors, including thrombosis resulting from interaction between PPIs and clopidogrel, and the risk of intestinal and pulmonary infections (Vakil, 2009). Therefore, according to the American Food and Drug Administration recommendations, IPP challenge should be always preceded by careful, individualized risk assessment, and its duration should take no longer than 1 to 2 weeks.

We are well aware of several limitations which should be considered during interpretation of our findings. These potential flaws include: (a) small size of examined group, (b) lack of the control group, (c) possibility of confounding placebo effect (Eckley et al., 2008), (d) administration of low (single) standard dose of omeprazole and relatively short duration of the therapy, (e) the lack of gold diagnostic standard of LPR which precludes the verification of PPI challenge accuracy, and (f) pharyngeal gargling and physiotherapy which could mask the influence of PPI on therapeutic outcome.

In conclusion, this study revealed that six weeks therapy
with omeprazole, accompanied by pharyngeal gargling and physiotherapy attenuates phoniatic symptoms of LPR and improves laryngeal morphology and function. Moreover, laryngovideoendoscopy still remains a principal tool in the diagnosis of LPR at the current state of knowledge (Park et al., 2005) and therapeutic response to empiric administration of IPP constitutes the important diagnostic criterion of this condition.

REFERENCES


