

Practical Considerations for Dysphonia Caused by Inhaled Corticosteroids

César A. Galván, MD, and Juan Carlos Guarderas, MD

CME Activity

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Abstract

Inhaled corticosteroid (ICS) therapy has become standard in the treatment of asthma. A common local adverse effect of ICS therapy is dysphonia, which has been reported to affect 5% to 58% of patients. Although causes of dysphonia associated with ICS therapy have been underinvestigated, it may result from deposition of an active ICS in the oropharynx during administration, which then causes myopathy or a mucosal effect in the laryngopharynx. Use of ICS should be considered during any evaluation of dysphonia. We recommend using the lowest effective dosage of ICS, administering medication with a spacer, gargling, rinsing the mouth and washing the face after inhalation, and washing the spacer. If dysphonia develops despite these interventions, ICS use should be suspended until symptoms resolve, provided that asthma control is not compromised.

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Dysphonia is a disorder characterized by altered vocal quality, pitch, loudness, or effort that impairs social and professional communication. It can deteriorate quality of life by affecting emotional, physical, social, and work function.^{1,2}

Dysphonia is an important but underrecognized adverse effect of numerous medications, with a lifetime prevalence of 29.9% in adults aged 65 years or younger.³ Women are more frequently affected than men (female to male ratio, 3:2).⁴ The prevalence of dysphonia is higher in individuals

who use their voice extensively in their profession; for example, 31% of telemarketers and 58% of teachers are affected.⁵ The economic burden of dysphonia is substantial. An estimated 7.2% of the general population misses work for at least 1 day because of voice problems; this represents approximately \$2.5 billion in annual work productivity lost in the United States.⁶ Therefore, dysphonia may be considered a public health challenge.

Warfarin sodium, thrombolytic agents, and phosphodiesterase-5 inhibitors can induce dysphonia by causing vocal fold hematomas⁷; biphospho-

From the Clinical Immunology and Allergic Diseases Division, Hospital Nacional Guillermo Almenara Iri-goyen, Lima, Perú (C.A.G.); and the Department of Otolaryngology-Head and Neck Surgery/Audiology, Mayo Clinic, Jacksonville, FL (J.C.G.).



FIGURE. Laryngoscopic image in a patient with asthma who recently started inhaled corticosteroid therapy and reported dysphonia. Note posterior bowing of the vocal cords. After performing the work-up for dysphonia, we concluded that this change was due to inhaled corticosteroid therapy.

nates can cause chemical laryngitis; and angiotensin-converting enzyme inhibitors can produce cough followed by dysphonia. Antihistamine, diuretic, and anticholinergic agents have a drying effect on the laryngopharyngeal mucosa.⁸ Danazol and testosterone can alter sex hormone production or use, or both, causing dysphonia. Of importance, the widely used classes of inhaled medications, in particular inhaled corticosteroids (ICS), can cause dysphonia, most likely via a myopathy or mucosal effect on the laryngopharynx (Figure).

It is well known that ICS therapy is the cornerstone of long-term treatment of asthma. However, ICS can cause systemic and local adverse effects. In addition to the widely studied systemic adverse effects of corticosteroids, dysphonia, oropharyngeal candidiasis, and pharyngitis are the most common local adverse effects related to ICS therapy. Therefore, clinicians must consider the risks and benefits of this treatment.

In this article, we review the literature pertaining to the incidence of dysphonia associated with ICS therapy, the potential mechanisms of the disorder, and relationships between dysphonia development and ICS dosage or administration devices. In addition, we provide some practical recommendations for patients using ICS.

INCIDENCE OF DYSPHONIA

Inhaled corticosteroid therapy has become the mainstay treatment of bronchial asthma.⁹ One of the

most common local adverse effects of ICS therapy is dysphonia, with an incidence that reportedly varies from 5% to 58%. In 1974, Williams et al¹⁰ described an incidence of transient dysphonia in 55% of patients who received treatment using triamcinolone acetonide aerosol. In 1993, Dong et al¹¹ reported that 8 of 100 patients with asthma who received beclomethasone propionate had dysphonia. In 1995, Williamson et al¹² reported dysphonia in 58% of patients using pressurized aerosol ICS preparations, compared with 13% of controls. In 2000, Lavy et al¹³ confirmed dysphonia via videostrobolaryngoscopy in 58% of patients who were receiving ICS therapy. More recently, Rachelefsky et al¹⁴ analyzed data from 23 studies published from 1966 through 2004 and determined that, compared with placebo, ICS at all dosages was associated with a 5.2-fold greater risk of dysphonia.

The wide range of incidence rates in these studies likely was due to methodologic factors, dosage variability, and how the diagnosis was made, which included self-reported questionnaires, telephone surveys, clinical diagnoses, endoscopic examinations, and histologic analyses of biopsy samples. Bearing in mind the limitations of the described studies, we believe that dysphonia caused by ICS therapy is not rare and should be considered a frequent cause of dysphonia.

MECHANISMS OF DYSPHONIA

Causes of dysphonia associated with ICS therapy have been poorly investigated, and the origins of dysphonia may have multiple confounding factors. Patients with asthma tend to have longer pauses between speech segments, pronounce fewer syllables per breath, and require more time in nonspeech ventilatory activity.¹⁵ In 1983, Williams et al¹⁵ identified bowing in the vocal folds and proposed a possible association between dysphonia and ICS therapy. Subsequently, they postulated that this bowing was due to a bilateral adductor myopathy induced by local deposition of topical corticosteroids. Although Babu and Samuel¹⁶ in 1988 reported similar findings as those of Williams et al,¹⁵ in other studies, vocal cord bowing was rarely found.¹⁷

Lavy et al¹³ described 22 patients with ICS-associated dysphonia who underwent videostrobolaryngoscopy and an objective acoustic analysis. Seventeen of the 22 were affected by dysphonia on a daily basis: 9 had some evidence of poor vocal fold apposition, and supraglottic hyperfunction was identified in 8. Mucosal quality abnormalities were identified in 13 patients. The mucosal wave was difficult to evaluate; however, the authors identified 2 patients with mucosal wave asynchrony. Insofar as speech evaluation, they noted cycle-to-cycle irregularity of 39% (mean, range between 2%-94%), and

the maximum phonation time was reduced in 16 patients. The individual analysis found no correlation between the degree of vocal cord apposition and the speech evaluation findings. The authors suggested that atrophy with bowing was not likely the primary cause of dysphonia. Although they noted that the primary cause was difficult to establish because of the various findings, they maintained that corticosteroids had a direct effect on the mucosa or on the mucus-secreting glands of the ventricles or the trachea.

Some studies have found that ICS use predisposes to development of an inflammatory infiltrate; however, this does not necessarily have a clinical correlate. In a prospective observational study of 50 patients,¹⁸ more inflammatory infiltrate was identified in ICS users compared with nonusers; however, pharyngeal erythema was not correlated with an inflammatory infiltrate.

Dysphonia associated with ICS use likely results from deposition of active ICS in the oropharynx during administration of the medication. However, taking into account the studies discussed earlier, we believe that a specific cause or mechanism of this disorder has not yet been elucidated.

DOSAGE AND DELIVERY OF ICS

Budesonide, beclomethasone, and fluticasone are associated with similar rates of dysphonia as an adverse effect, although initial reports have suggested a higher risk of dysphonia with fluticasone propionate than with beclomethasone¹⁹ or budesonide.²⁰ In another study, treatment with 200 μ g of mometasone administered using a metered-dose inhaler (MDI) was associated with fewer instances of dysphonia than was 168 μ g of MDI-administered budesonide.²¹ However, a more recent meta-analysis of randomized controlled trials demonstrated that budesonide was associated with the highest risk of dysphonia when compared with beclomethasone and fluticasone. When comparing ICSs at high dosages, budesonide was associated with the greatest risk of dysphonia.¹⁴ The novel synthetic ICS ciclesonide has demonstrated no large differences in occurrence of dysphonia as an adverse effect when compared with placebo. However, further research is needed to establish the probably lower risk of dysphonia between ICSs.²²

Dysphonia may be affected by the method used to administer medication. Selroos et al²³ described 154 patients who received ICS therapy for 2 years via an MDI and then switched to administration via a dry-powder inhaler (DPI). They noted that the frequency of dysphonia decreased from 21% to 6%. This change may be attributable to differences in vocal cord positioning when using a DPI compared with an MDI. The meta-analysis of randomized con-

trolled trials by Rachelefsky et al¹⁴ found that ICS MDI devices were associated with a 5-fold greater risk of dysphonia when compared with placebo MDI devices, whereas the ICS DPI devices had a 3-fold greater risk vs placebo DPI devices. Insofar as dysphonia in patients receiving combined corticosteroid and bronchodilator therapy, Mirza et al²⁴ described voice and laryngeal changes in 5 patients who switched from corticosteroid and bronchodilator therapy administered separately to concurrent administration. Most patients had areas of hyperemia and a plaque pattern on the surface mucosa. The combination therapy was stopped to assess reversibility of the mucosal lesions. Twelve weeks after stopping the combination therapy, patients underwent a laryngeal examination; 3 showed substantial improvement in lesions, and 2 seemed to have complete recovery. More recently, a systematic review of randomized controlled trials by Frois et al²⁵ found no differences in dysphonia or other local adverse effects when comparing fluticasone or budesonide combined with long-term bronchodilator therapy.

CONCLUSION AND RECOMMENDATIONS

Inhaled corticosteroids are associated with an increased occurrence of dysphonia. Any evaluation of dysphonia should consider use of ICS or other medications as an adverse effect, include a thorough examination of the larynx, and rule out vocal cord nodules, posttussive trauma, and gastroesophageal reflux. Well-designed studies, particularly prospective studies, must be conducted to identify clinical, endoscopic, functional, and histopathologic correlates of ICS-associated dysphonia.

Because ICS therapy is the cornerstone of asthma treatment, we recommend using the lowest effective dosage of ICS and administering it with a spacer to decrease oropharyngeal deposition of inhaled aerosols. After using a spacer, it must be washed with tap water and allowed to air dry. Patients should be instructed to rinse the mouth, gargle, and wash the face after inhalation. Instructions should be provided on the proper method of inha-

TABLE. Practical Recommendations to Reduce Dysphonia Caused by Inhaled Corticosteroids

Use the lowest dosage of inhaled corticosteroid that maintains asthma control
Use a spacer, wash it with tap water, and allow it to air dry after use
Rinse the mouth, gargle, and wash the face after inhalation
Instruct patients in the proper method of inhalation

lation. Some of these recommendations are pragmatic expert opinions that need future research (Table). If dysphonia develops despite these interventions, ICS use should be suspended until symptoms resolve, provided that asthma control is not compromised.

Abbreviations and Acronyms: DPI = dry-powder inhaler; ICS = inhaled corticosteroid; MDI = metered-dose inhaler

Correspondence: Address to César A. Galván, Avenida San Luis 2736, Lima 41, Perú (cegals8@hotmail.com).

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