Steroid Inhaler Laryngitis

Dysphonia Caused by Inhaled Fluticasone Therapy

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Objective: To describe a condition that is referred to as steriod inhaler laryngitis, a clinical entity that is caused by the use of inhaled fluticasone propionate and manifested by dysphonia, throat clearing, and fullness.

Design: Case series.

Setting: An outpatient clinic of an academic referral center.

Patients: The study population consisted of 20 patients with reactive airway disease and dysphonia who were receiving inhaled fluticasone therapy and who were diagnosed as having steroid inhaler laryngitis during the period from January 1998 to June 2000.

Intervention: Cessation of inhaled fluticasone therapy when possible, as well as treatment of other underlying causes of dysphonia, such as laryngopharyngeal reflux and infectious processes.

Main Outcome Measure: The resolution of dysphonia with cessation of inhaled fluticasone therapy.

Results: Patients with steroid inhaler laryngitis were found to have laryngeal findings ranging from mucosal edema, erythema, and thickening to leukoplakia, granulation, and candidiasis. Patients with more severe mucosal findings were more likely to have laryngopharyngeal reflux as well. Resolution of dysphonia occurred only after discontinuation of the inhaled fluticasone therapy.

Conclusions: Steroid inhaler laryngitis is a form of chemical laryngopharyngitis induced by topical steroid administration. Symptoms and physical findings mimic laryngopharyngeal reflux, but only respond completely to discontinuation of the inhaled steroid therapy. The otolaryngologist should be familiar with this cause of dysphonia.


The otolaryngologist—head and neck surgeon is frequently asked to evaluate a patient with the main complaint of dysphonia. There are many causes for dysphonia, including neoplasm, trauma, vocal abuse syndromes, neuromuscular disorders, functional voice disorders, and chemical injury such as laryngopharyngeal reflux (LPR). In my practice, I have become increasingly aware of another type of chemical injury to the larynx that can result in dysphonia, especially in patients with reactive airway disease (RAD) who are being treated with inhaled fluticasone propionate.

Fluticasone propionate (Flovent) has become the most commonly prescribed steroid inhalent for patients with asthma and RAD because of its potency and safety margin. It also is the most potent steroid used in inhaled form, with activity 9 times greater than that of flucinolone acetonide, 2 to 5 times greater than that of budesonide, and twice that of beclomethasone dipropionate.1-3 It has a greater topical potency, longer tissue retention, and a longer elimination half-life than beclomethasone. Orally administered medication is rapidly metabolized on the first pass through the liver, resulting in less than 1% oral bioavailability compared with 11% for budesonide, 20% for flunisolide, and more than 80% for prednisolone.4 The Physicians’ Desk Reference reports the incidence of dysphonia to be approximately 1% to 8%, a rate that is similar to that of other inhaled steroids, with increasing frequency at higher dosages.5 Clinical studies have reported the incidence of dysphonia with all inhaled steroids to be as high as 55%.6-11

An increasing number of patients who are using fluticasone are being referred for evaluation of dysphonia. This type of dysphonia is not responsive to treatment of other causes of dysphonia, but improves with cessation of inhaled fluticasone therapy. The spectrum of vocal cord changes...
PATIENTS AND METHODS

Records were reviewed retrospectively to January 1998, and cases were evaluated prospectively from June 2000. I evaluated all patients who were referred for a primary diagnosis of dysphonia in the tertiary care otolaryngology–head and neck surgery clinic at Emory University, Atlanta, Ga. The patients’ records were reviewed for demographic data, comorbidities, time at onset of dysphonia and other laryngopharyngeal symptoms, medications used (specifically inhalants) and the date of initiation of treatment, upper aerodigestive tract physical findings, diagnostic tests performed, and outcomes of treatment.

that has been seen is more extensive than has been described in previous publications on dysphonia resulting from inhaled steroid treatment,\textsuperscript{14,15} ranging from minimal to severe. In 2 cases, the vocal fold changes were severe enough to prompt direct laryngoscopy and biopsy, with these cases occurring before these changes were recognized as part of a clinical entity that is referred to as \textit{steroid inhaler laryngitis} (SIL). The severity of the vocal cord mucosal changes is likely a result of the greater potency of fluticasone compared with other inhaled steroids. In many of the patients with severe vocal cord changes due to SIL, there may be a synergistic effect with LPR. Herein, representative cases are presented and the various findings of SIL are described.

REPORT OF CASES

CASE 1

In February 1998, a 50-year-old female speech therapist presented with a 3-month history of hoarseness and vocal fatigue. She had experienced exacerbation of her asthma during an upper respiratory infection, for which she had been treated with 2 courses of antibiotics. At that time, fluticasone therapy (220 µg twice daily) was also initiated. The dysphonia began some time during the treatment for the upper respiratory infection. Other symptoms included frequent throat clearing and postnasal drip. The patient was treated with voice rest, with minimal improvement. Examination of her larynx revealed bilateral severe vocal cord and arytenoid hyperemia, as well as interarytenoid mucosal thickening and leukoplakia (Figure 1). She received a diagnosis of LPR and was treated with omeprazole sodium (20 mg twice daily) and behavioral modifications. There was mild improvement, but the patient continued to have daily hoarseness. The dosage of omeprazole sodium therapy was increased to 60 mg/d, with further mild improvement but no resolution of the hoarseness. After 5 months of treatment, the patient underwent a 24-hour pH study (while not taking omeprazole) that confirmed pathological reflux at the upper esophageal sphincter (pH<4 for 1.8% of study). The dosage was then increased to 80 mg/d, and ranitidine hydrochloride (300 mg to be taken at bedtime) was added to the regimen. After 1 year of treatment, the patient continued to have hoarseness and abnormal laryngeal findings. A 24-hour pH study with an intragastric probe revealed almost complete acid suppression during therapy (intragastric pH<4 for 1.2% of study). Examination of the larynx at that time revealed similar findings, as well as slight bilateral bowing of the vocal cords, which was thought to represent the coexistence of muscle tension dysphonia.

During this period of treatment, the patient had 2 mild exacerbations of her RAD. Since the LPR treatment was not resolving her hoarseness completely, and because of the temporal relationship between symptom onset and the start of fluticasone therapy, the therapy was discontinued and the patient’s medication was changed to oral montelukast sodium (Singulair). She had resolution of her hoarseness within 4 weeks and has not had a recurrence in more than 2 years. She has been on a therapeutic maintenance regimen of low-dose proton pump inhibitors for her LPR.

CASE 2

In January 1998, a 51-year-old man, 8 months after undergoing a single left lung transplantation for idiopathic pulmonary fibrosis, was referred for evaluation of hoarseness and cough. He had developed a nonproductive cough 1 month earlier and been started on a regimen of fluticasone propionate (220 µg twice daily). The dosage was increased to 440 µg twice daily less than 1 month later. The patient subsequently developed hoarseness and throat clearing in addition to his cough. He did admit to some heartburn. Laryngeal examination revealed diffuse glottic erythema, granularity and leukoplakia of the vocal cords, and pale, thickened interarytenoid mucosa (Figure 2A). The diagnosis of LPR was made, and the patient began a regimen of omeprazole sodium (20 mg twice daily) and behavioral modifications. Over the course of the next several months of omeprazole sodium therapy, at a dosage of up to 60 mg/d, he had mild to moderate improvement of his cough and hoarseness, while his heartburn resolved. At times, the omeprazole therapy was discontinued, and the patient’s symptoms quickly worsened. The findings of
laryngeal examination never improved significantly. In January 1999, the patient underwent direct laryngoscopy and biopsy of the vocal cords because of persistent leukoplakia and granulation. Pathological examination revealed only granulation and acute inflammation, with no evidence of dysplasia or fungal elements. The patient’s hoarseness and other symptoms persisted. In April 1999, he underwent a pH study, the findings of which confirmed the presence of pathological reflux. Since his symptoms did not resolve with aggressive reflux therapy, the possibility that the steroid inhalers were contributing to his hoarseness was entertained, and the fluticasone therapy was discontinued. Within approximately 6 weeks, he had significant improvement of his voice and almost complete resolution of the leukoplakia and granulation, as well as reduction of the vocal cord erythema (Figure 2B). He has continued intermittent use of proton pump inhibitors and his voice has returned to normal.

**CASE 3**

In May 2001, a 41-year-old woman was referred for evaluation of chronic sinusitis, at which time she was noted to have a deep, hoarse voice. She admitted to having been hoarse for approximately 4 years. She had severe RAD and had been using fluticasone propionate (880 µg twice daily) for 4 years, in addition to salmeterol xinafoate (Serevent) and ipratropium bromide (Atrovent). She was also taking omeprazole sodium (20 mg/d) for gastroesophageal reflux, which had been documented by a pH study. She had had multiple previous episodes of oral candidiasis as well. Examination of her larynx revealed diffuse laryngeal granularity, erythema, and thickening of the mucosa, with diffuse punctate white patches consistent with laryngeal candidiasis (Figure 3A). Her vocal cord mobility was also slightly reduced bilaterally, although this did not affect the glottic airway. Because of her severe RAD, her pulmonologist did not believe that reducing the dosage of the fluticasone therapy was in her best interest. Two weeks of fluconazole therapy was therefore prescribed. Her LPR was more aggressively treated with esomeprazole magnesium (40 mg/d), and she was instructed regarding behavioral modifications. Follow-up examination of the larynx at 1 week and 1 month after initiation of treatment revealed resolution of the candidiasis, with improvement but persistence of the edema, erythema, and granularity (Figure 3B).

**CASE 4**

In April 2001, a 58-year-old woman was referred for a 2-month history of hoarseness. Two months before the onset of the hoarseness, fluticasone propionate therapy (88 µg twice daily) had been initiated. Immediately before the hoarseness began, the dosage of the fluticasone propionate therapy was increased to 220 µg twice daily. Examination of the vocal cords revealed mild vocal cord congestion (Figure 4). The fluticasone therapy was discontinued, and the patient’s voice improved during the next month.

**RESULTS**

Twenty patients were identified who were diagnosed as having SIL during the study period from January 1998 to September 2001. Approximately 1 to 2 new cases per month are now recognized and diagnosed as SIL resulting from inhaled fluticasone therapy. All the patients received a diagnosis of RAD, with most having other comorbidities, including LPR or gastroesophageal reflux. Most patients, especially those who received treatment earlier in the course of this review, were treated for other suspected causes of dysphonia before the role of inhaled fluticasone therapy in the pathogenesis of the problem was recognized. Two patients underwent microlaryngoscopy with vocal cord biopsy to rule out dysplasia or malignancy prior to definitive diagnosis. All patients
had significant or total improvement of their voice after cessation of inhaled fluticasone therapy, usually within 4 to 6 weeks. Unfortunately, some patients could not discontinue the use of inhaled fluticasone owing to the severity of their RAD.

All patients had the primary symptom of dysphonia, with varying severity. Other symptoms included frequent throat clearing and throat fullness. Physical findings ranged from mild laryngeal changes, including edema, erythema, and mucosal thickening, to more dramatic changes, including leukoplakia, granulation, and laryngeal candidiasis.

Steroid inhalers are the first line of treatment for RAD of all severity. It has long been known that one of the most common adverse effects of inhaled steroid therapy is irritation of the upper aerodigestive tract. Common symptoms include pharyngitis, hoarseness, throat clearing, and cough. These symptoms occur with all steroid inhalant preparations, and appear to be dose related. It is likely that the steroid, not the propellant, is responsible for the local adverse effects in the laryngopharynx. Patients inhaling beclomethasone were 5 times more likely to have hoarseness than patients treated with the propellant without the steroid. The Physicians’ Desk Reference reports the incidence of hoarseness for the various steroid inhaler preparations to range from 1% to 9%, compared with 0 to 3% for nonsteroid inhalers. Clinical studies show the incidence of hoarseness to be much higher, occurring in as many as 55% of patients who use steroid inhalers. Of the inhaled steroids, fluticasone has a greater topical potency and greater tissue retention and half-life. Clinical reports of the incidence of dysphonia with fluticasone are limited, and clinical studies report an incidence that ranges from only 2% to 6%. The onset of dysphonia can occur at any time during fluticasone therapy, but in the patients described herein it most commonly manifested shortly after the onset of treatment, as in the first 3 case reports, or after an increase in the dosage, as in the fourth case.

The physical changes that are seen in the larynx of patients using inhaled fluticasone range from minimal to severe. Mild physical findings include edema and erythema. Moderate changes include mucosal thickening and vocal cord bowing. The most dramatic changes include leukoplakia, granulation, and laryngeal candidiasis. Many of these findings can also be seen with LPR, and differentiating these 2 possible pathogenetic factors can be difficult if one is not familiar with SIL, as happened in the first 2 cases. Physical findings may be minimal in patients with dysphonia caused by the use of steroid inhalers, with only mild edema of the vocal cords, as in case 4. The changes appear to be the result of a mucosal inflammatory reaction to the steroid. Two patients in our series underwent biopsy of severely diseased vocal cords, and pathological examination of the specimens revealed only acute inflammation and granulation, as in case 2.
In 1983, Williams et al. described 14 patients whose dysphonia was attributed to the use of steroid inhalers (budesonide, beclomethasone, and betamethasone). Nine of these patients were reported to have adductor palsy of the vocal cords, manifesting as vocal cord bowing. The cause was theorized to be a local steroid myopathy. All 14 patients recovered normal vocal cord movement and appearance after they discontinued using the steroid inhaler, and they had a recurrence when they switched to a different steroid preparation. Hoarseness was thought to be due to candidiasis in 3 patients and to psychogenic causes in 2 patients (because no abnormalities were found on their vocal cord examinations). Of interest, aside from the bowing and the candidiasis, the results of laryngeal examinations in all 14 patients were described as normal, with no mucosal abnormalities reported. In case 1, the patient had significant mucosal changes at presentation but did not develop vocal cord bowing until approximately 1 year after starting inhaled fluticasone therapy. At the time, the bowing was incorrectly attributed to muscle tension dysphonia rather than a manifestation of SIL. The prominent mucosal changes seen in this group of patients may be attributable to fluticasone’s greater potency and tissue affinity compared with other inhaled steroid preparations.

Babu and Samuel evaluated the upper aerodigestive tracts of 48 consecutive patients who were receiving inhaled steroid therapy (beclomethasone). While 20% of patients admitted to voice changes, 46% had “congested erythematous vocal cords” on examination, and 8.5% were reported to have adductor palsy, with vocal cord bowing. Williamson et al. used a questionnaire to determine the prevalence of upper aerodigestive tract symptoms in 255 patients who were using inhaled steroid preparations: 58% reported voice or throat symptoms, with a 39% incidence of hoarseness and a 40% incidence of throat clearing. The symptoms were found to increase when the dosages of inhaled steroid therapy were higher.

Oral and pharyngeal candidiasis is a known adverse effect of inhaled steroid therapy, with an incidence of up to 13% using the criteria of typical physical findings and positive culture results. Cultures that are positive for Candida have been found in up to 50% of cases involving patients who use steroid inhalers, irrespective of symptoms and physical findings. Findings of clinical infection include erythema and edema of the mucosa, with white exudative patches, as seen in patient 3 (Figure 3A). Treatment involves the use of oral antifungal agents. Reduction or cessation of inhaled steroid therapy should be undertaken if the condition does not clear up with antifungal therapy. The use of spacers to reduce the oral deposition of steroid appears to reduce the occurrence of oral candidiasis but not the degree of laryngopharyngeal symptoms, and may increase the symptoms by delivering a larger amount of steroid to the larynx and pharynx. Fairfax et al. reported a case of laryngeal aspergillosis resulting from inhaled fluticasone therapy. Treatment involved cessation of inhaled fluticasone therapy and aggressive antifungal therapy.

The most severe cases that were experienced in the patient population described herein involved the coexistence of LPR with SIL. The laryngeal changes in SIL are similar to the changes that can be found in patients with LPR, including edema, erythema, and interarytenoid mucosal thickening. Before SIL was recognized as a distinct clinical entity, all these patients were treated aggressively for LPR, with only partial resolution of symptoms. Only after the patients discontinued using the steroid inhaler did they have complete resolution of their throat symptoms, especially their hoarseness. Adequate treatment of severe LPR requires cessation of steroid inhaler therapy, if possible, and aggressive treatment of underlying LPR, if present. Mild symptoms of SIL with mild vocal cord changes were adequately treated with cessation of their inhaled steroid therapy. It is likely that most patients with mild symptoms of SIL do not seek medical attention for their laryngopharyngeal symptoms.

**CONCLUSIONS**

Steroid inhaler laryngitis is a distinct clinical entity with symptoms localized to the upper aerodigestive tract, including hoarseness, throat clearing, and cough. Laryngeal findings can range from minimal to severe. Patients with severe laryngeal changes are more likely to have significant LPR coexistent with SIL. Adequate treatment involves cessation or reduction of inhaled steroid therapy and treatment of underlying LPR, if present. The otolaryngologist needs to be able to recognize this condition and be familiar with its treatment. Any workup of dysphonia requires a thorough history of inhaler use.

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