

Inhaled Corticosteroids and Voice Problems. What Is New?

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Summary: Background. Voice problems are the most common and most annoying local side effect of inhaled corticosteroids (ICS), affecting not only patients' treatment compliance but also their quality of life. The literature is very poor regarding prevalence, mechanism, prevention, and management of voice problems attributed to ICS use and especially for the new ICS, ciclesonide. Prevalence of dysphonia seems to be less common with the use of ciclesonide and beclomethasone dipropionate.

Method. We conducted a bibliography review based on recently published data, including data from the recently introduced ICS, ciclesonide, which are lacking in previous reviews.

Results. Very little improvement, based on limited number of new papers published during previous years without any direct comparison between available ICS, has been made in our understanding of ICS local side effects.

Conclusion. Our understanding concerning basic information of ICS effects on voice still remains poor, and further investigation is needed to have a better understanding on epidemiology, predisposing factors, mechanisms, prevention, and treatment of voice problems attributed to ICS.

Key Words: Inhalation–Asthma–Dysphonia–Voice–Hoarseness.

INTRODUCTION

Asthma is a chronic inflammatory disorder of the lower airways, with a worldwide distribution affecting both genders and all ages. The prevalence of asthma is increasing worldwide.^{1,2} It is estimated that at least 300 million people currently have asthma, and it is expected that more than 100 million will have been added by 2025.^{3,4} Despite the progress that has been made in the diagnosis and treatment of asthma, it continues to be one of the most underdiagnosed and undertreated diseases, resulting in high morbidity and disability rates.

Inflammation of the bronchi is the main underlying cause of airway hyperreactivity and bronchoconstriction and therefore of asthma symptoms. Corticosteroids are the cornerstone of asthma management as they are the most potent antiinflammatory agents currently available. Inhaled corticosteroids (ICS) are recommended, in national and international guidelines, as first-line therapy at low doses for mild persistent asthma and as the preferred therapy at medium doses or in combination with a long-acting β_2 -agonist for moderate persistent asthma.^{3,4} Combination therapy with high doses of ICS is recommended only for patients with severe persistent asthma.^{5,6}

ICS are preferred to oral administration as they have been associated with significantly fewer side effects. Systemic side effects with conventional ICS doses are negligible, but concern is needed for systemic and local side effects when higher doses are used.

Systemic side effects of ICS are mainly attributed to swallowing of the topical deposited inhaled ICS.

Voice problems and especially dysphonia continue to remain the main local side effect of ICS, despite the development of new ICS molecules and new, sophisticated delivery systems.

The purpose of our study was to review the current literature by looking for new information that can improve our understanding in preventing and managing ICS-related voice problems.

METHODS

A literature search was performed concerning ICS and voice disorders using the following databases: PubMed, EMBASE (from 1980 to October 2015), and Cochrane Library (from 1993 to 2015). The keywords used for the study were “inhaled corticosteroids and voice problems,” “treatment and dysphonia,” and “dysphonia.” Articles, letters, summaries, and dissertations published in English were included in our search. Additional information was gathered from references cited in the identified publications and products' package insert. Particular emphasis was given to original articles and, on a secondary basis, to books and reviews. One hundred four papers, related to our search, were identified and reviewed. Only studies reporting appropriate information on our study design were included for review. Among these studies, there was one meta-analytic study⁷ and five reviews.^{8–11} Two reviews, one in Spanish and one in German, were excluded.

RESULTS

Local side effects of ICS

The most common local side effects of ICS are shown in [Table 1](#).

Although local side effects, compared with systemic ones, are not serious, they can affect the patient's quality of life, treatment compliance, and most importantly, they can mask symptoms of a more serious disease. For example, dysphonia and hoarseness are very common local side effects of ICS, but they can

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TABLE 1.
Local Side Effects of Inhaled Corticosteroids^{11–13}

Hoarseness or Dysphonia
Cough
Aphonia
Dry, sore throat
Voice misuse or throat clearing
Candidiasis
Pharyngitis
Perioral dermatitis
Tongue hypertrophy
Sensation of thirst

be cardinal symptoms of laryngeal cancer. It is of capital importance in every patient with persistent hoarseness, especially after cessation of ICS therapy, to perform an in-depth investigation for the exclusion of such a possibility.

Local side effects of ICS are a result of deposition of the active form of the drug in the pharyngolaryngeal area.

Dysphonia

Whether hoarseness or huskiness and dysphonia are separate symptoms is a matter of debate. Most of the investigators believe that the term dysphonia covers all symptoms related to voice problems as a consequence of ICS use, and from now and on, in this paper, the term dysphonia will be used to describe the whole spectrum of voice disturbances related to ICS use.

Incidence of dysphonia

Dysphonia, with or without candidiasis, is by far the most frequent local side effect of ICS. The prevalence of dysphonia varies significantly among studies, depending on the definition of the term, the type of the study, and especially the method that was used to detect dysphonia (questionnaire or inspection).^{14,15} The highest prevalence rates are found in studies where symptom-based questionnaires were used, and the lowest were found in studies where clinical and laboratory examinations (inspection) were performed. Generally, the more precise the applied diagnostic criteria were used, the lower prevalence of dysphonia was observed. For example, recording hoarseness and dysphonia as different symptoms results in a lower prevalence of dysphonia. In general, most of the well-organized studies in which inspection was included among the basic diagnostic criteria estimate the prevalence of dysphonia at 5%–10%.

A number of factors have been recognized as contributing in the appearance of dysphonia (Table 2).

The prevalence of dysphonia is not the same with different types of ICS. For reasons related mainly to pharmacological characteristics of each compound, the prevalence of dysphonia varies significantly among currently available ICS. Table 3 shows the prevalence of dysphonia of different ICS as it has been reported in their Summary of Product Characteristics or in clinical trials.

A number of factors influence where and how much drug is deposited in the airway and upper aerodigestive tract. These

TABLE 2.
Factors Contributing to the Appearance of Dysphonia

1 Active compound of ICS
2 Type of ICS (active drug or prodrug)
3 Potency of ICS
4 Dosage and frequency of ICS use
5 Patient's compliance and right use of product delivery device
6 The size of the delivered particles
7 The velocity of the delivered particles
8 The type of the delivery system (DPI, MDI)
9 The use of spacer

include size of particle, type of drug (active or prodrug), velocity and type of delivery system, and technique of inhalation.

Effect of particle size

The size of the particles is of capital importance for the drug to reach the final target, which is the lungs and especially the small airways. The smaller the particle size, the highest deposition on the airways and lungs is observed, and the largest the particle size, the maximal deposition in the oropharynx and larynx is. Particles with diameter <5 μm are most likely to be deposited on the small airways, whereas particles with diameter >5 μm are mainly deposited in the oropharynx and larynx.²³ The particle sizes are related and dependent on the propellant used for drug dissolution. Chlorofluorocarbons based metered-dose inhaler (CFC-MDI) devices give larger particles and achieve lung deposition of approximately 10%–20%,²⁴ whereas hydrofluoroalkane (HFA)-based devices give smaller particles, achieving 50% lung deposition.²⁵

Depending on the particle size, oropharyngeal deposition can be up to 60% of delivered dose.¹² The size of the particles varies significantly among different ICS available for use in today's practice, as shown in Table 4.

Effect of type of ICS

The type (active drug or prodrug) of ICS is related to the incidence of dysphonia, as prodrugs that are activated in the lungs seem to produce less local side effects in the laryngopharynx. Some ICS, including fluticasone propionate and budesonide, are inhaled in their pharmacologically active form, whereas others, like ciclesonide and beclomethasone dipropionate, are inhaled as inactive compounds and are converted by lung esterases to

TABLE 3.
Prevalence of Dysphonia for Inhaled Corticosteroids Available Today

Inhaled Corticosteroid	Dysphonia Prevalence (%)
Fluticasone propionate ¹⁶	3–8
Budesonide ¹⁷	1–6
Beclomethasone dipropionate ^{18,19}	<2
Triamcinolone acetonide ²⁰	1–3
Ciclesonide ^{21,22}	0–2

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