



ORAL MANIFESTATIONS IN ASTHMATIC PATIENTS USING INHALATION THERAPY – A REVIEW

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ABSTRACT

Asthma is a chronic inflammatory disorder of the airways characterized by recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. The objectives of therapeutic interventions for asthma include prevention and control of symptoms, reduction in the frequency and severity of asthma exacerbations, and reversal of airflow obstruction. Most asthma drugs are inhaled using various forms of inhalers or nebulizers. Inhalation has long been established as an effective way to deliver drug to the lungs, as inhaled medicines are delivered directly to the airways and allow a smaller dose to be administered leading to a quicker onset of action and fewer side – effects. High dosage and long duration of inhalation therapy has been closely linked with several adverse effects on oral tissues. Hence this review highlights the effects of inhalation therapy on oral tissues along with recommendations for prevention.

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways characterized by attacks of bronchoconstriction causing shortness of breath, coughing, chest tightness, and rapid breathing.¹ It is a respiratory disorder associated with high incidence, prevalence and mortality rate. Asthma currently affects 300 million people worldwide and an additional 100 million people are estimated to get affected by 2025. It accounts for approximately one in every 250 deaths worldwide; annually, approximately 15 million disability – adjusted life years are lost because of the disease.²

Pathogenesis of asthma

Asthma usually begins in childhood or adolescence but can develop at any time in life. The basic defect in asthma lies in abnormal contractility of airway smooth muscle, giving rise to variable airflow obstruction, and the common symptoms of intermittent wheeze and shortness of breath.³The obstruction to airflow is more pronounced during expiration. The causes of airway obstruction in asthma are bronchoconstriction led by the contraction of the bronchial smooth muscles, inflammation of the bronchial walls, and increase in mucus secretion. The air flow obstruction is usually reversible, but complete it may not be reversible in all the cases. It may be an acute life-threatening attack or chronic with mild to moderate or severe symptoms.

Management of asthma

Management of asthma has two main objectives: to control and to reduce the airway inflammation, and reopen the airways. The management starts with avoidance of stimuli, hyposensitisation of allergens and oxygen administration. Controlling the symptoms with anti – asthmatic medicines is the main component of management. Drugs that achieve the first objective are called controllers and those that achieve the second are called relievers.⁴

Controllers are medications that are taken daily on a long term basis to keep asthma under control mainly through anti – inflammatory effects. These include anti – inflammatory agents, long acting beta agonists (LABA) and leukotriene modifiers. Relievers are medications used on an as – needed basis, which act quickly to reverse bronchoconstriction and relieve its symptoms. They are also known as rescue medications and consist of short – acting beta – agonists (SABA), systemic corticosteroids and anticholinergic drugs. They relieve symptoms by relaxing the muscles that tighten around the airways. This action rapidly opens the airways, letting more air come in and out of the lungs.⁴

Inhalation treatment of asthma

The respiratory tract, however, has several mechanisms that protect it from the entry and deposition of particles. Aerodynamic filtration, reflexes such as cough and sneeze, and mucociliary clearance all contribute to the rapid elimination of inhaled soluble and particulate materials.⁵

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There are several groups of drugs useful in the treatment of asthma which are available by the inhaled route.⁵ These are discussed as follows:

Bronchodilators

Bronchodilators have been administered by inhalation for more than 50 years.⁵ The various bronchodilators include β_2 Sympathomimetics, Methylxanthines and Anticholinergic agents.

Adrenergic drugs cause bronchodilatation through β_2 receptor stimulation \rightarrow increase cAMP formation in bronchial muscle cell \rightarrow relaxation. They are the mainstay of treatment for reversible airway obstruction, but should be used cautiously in hypertensives, ischaemic heart disease patients and in those receiving digitalis. They are the most effective and fastest acting bronchodilators when inhaled.⁶

Atropinic drugs cause bronchodilatation by blocking M3 receptor mediated cholinergic constrictor tone; act primarily in larger airways which receive vagal innervation.⁶ Ipratropium bromide, an anticholinergic agent is also an effective bronchodilator, with few atropinic side effects in normal dosage. It is particularly useful in toddlers when the effects of beta agonists may be limited.⁵

The methylxanthines are also effective bronchodilators. Although they have been administered by inhalation, the oral or intravenous routes are preferred because these drugs irritate the airways.⁵

Sodium cromoglycate

This is an effective prophylactic agent for asthma. Its mode of action is not completely understood but it is a potent mast cell stabiliser. It is poorly absorbed and is only effective by inhalation. It is available as nebuliser solution, powder aerosol, and an aerosol and the doses which give equivalent effects are 20 mg by nebuliser or powder to 2 mg by aerosol.⁵

Corticosteroids

Glucocorticosteroids are the most potent antiinflammatory agents currently available for the treatment of asthma, but given systemically have many serious side effects.⁵ They 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 long-acting β_2 -agonists for moderate persistent asthma.⁷ Inhaled corticosteroids are believed to exert their effects after translocation into the nucleus of the respiratory epithelial cell and other cells in the airway, via the glucocorticoid receptors.⁸ Their clinical benefits include decreased asthma symptoms, fewer exacerbations, fewer hospitalizations, decreased airway hyperresponsiveness, improved pulmonary function, decreased exhaled nitric oxide, and fewer asthma-related deaths. Three delivery systems available for Inhaled Corticosteroids include: Nebulizers, Metered - dose inhaler (MDI), Dry - powder inhaler (DPI).⁵

Adverse effects of inhalation therapy

Inhaled corticosteroids are safe, and if properly administered have relatively few adverse effects.

Systemic adverse effects of Inhaled corticosteroids are dose – related. The more the drug deposited in the lung, the greater

the systemic absorption and the greater are the systemic adverse effects.

Local side effects

The most common oropharyngeal side effects associated with Inhaled corticosteroids are oropharyngeal candidiasis, dysphonia (hoarseness), pharyngitis (sore throat), and reflex cough. Local side effects that generally occur at low incidence include perioral dermatitis and tongue hypertrophy. The sensation of thirst after delivery of steroids is a more common effect but is likely secondary to pharyngitis and oropharyngeal candidiasis.⁹

Oropharyngeal candidiasis

Candidiasis or oral thrush is a fungal infection caused by any of the *Candida* species, of which *Candida albicans* is the most common. Oropharyngeal candidiasis is commonly associated with the use of inhaled corticosteroids. Approximately 10-20% of the inhaled corticosteroid reaches the lungs and the rest is deposited on the oropharynx.¹⁰ This occurs in terms of regular use of high-dose inhaled corticosteroids. Immunosuppressive potency of corticosteroids also plays a role in progression of candidiasis. Repeated contact of steroid inhalant on the oral mucosa can result in development of acute pseudomembranous candidiasis (oral thrush) because of fungal overgrowth in an area of localized immunosuppression.¹¹ Additionally, dry mouth caused by β_2 -agonists is also a key factor in the progression of candidiasis. This steroid – induced infection consists of colonies of *Candida* that appear as curdy white located commonly on the soft palate and oropharynx. Eventually the white precipitates peel off leaving behind an intensely erythematous and raw – looking area.¹¹ The lesions are usually asymptomatic. However, wiping the plaques reveals a red, raw or bleeding mucosal surface and patients may complain of burning sensation while taking spicy food.

Measures to prevent oropharyngeal candidiasis include use of an MDI with spacer device and mouth rinsing with water immediately after inhalation. Chewing sugar – free gums and use of sialogogues is recommended to prevent dry mouth which has an impact on the progression of candidiasis. Controlled use of topical antimycotics, such as nystatin may be effective against oral candidiasis. Mouthwashes with nystatin or amphotericin B are also effective for treatment of oropharyngeal candidiasis.¹⁰

Asthma and Dental Caries

Dental caries is a multifactorial disease which progresses through a complex mechanism that includes demineralization of the enamel by means of the organic acids produced by microorganisms in dental plaque. Researchers have reported an increased prevalence of caries in asthmatic children. Ersin *et al.* reported that medications used for asthma induce dental caries by decreasing pH of saliva and salivary flow rate. Ryberg *et al.* (1987) reported that the risk for caries progression increased through the decreased salivary flow rate and increased salivary levels of *Streptococcus mutans* and *Lactobacillus* in patients using β_2 agonists.¹⁰ Decreased salivary flow rate causes decrease in buffering capacity of saliva and the benefit of saliva in elimination of the fermented food from the oral environment cannot be gained.

Besides indirect side effects of asthma medications, fermentable carbohydrates present in asthma medications may also increase the risk for dental caries. Sugars like lactose monohydrate are added within the composition of some inhalers to promote the tolerance of the patient towards the taste of the medication. Frequent consumption of cariogenic drinks to remove the taste left by asthma medications in the mouth also increases the risk for caries. Ignorance of oral hygiene by patients due to their medical conditions and indulgent attitude of parents towards their children's sugar intake are among the factors that further promote dental caries.¹²

Individuals with medical problems and those considered to be at high risk for dental caries need special care and should be checked in less than 6 months. Parents should be incorporated into oral hygiene education of their children and, tooth brushing in preschool children should be performed under parental supervision. Patients should be informed about rinsing the mouth after each use of inhaler. It is also recommended to use fluoride – containing mouthwash after brushing of teeth.¹²

Asthma and Dental Erosion

Saliva is considered as one of the main neutralizing factors in the pathogenesis of dental erosion. McDerra *et al.*, Al-Dlaigan *et al.* and Sivasuthamparam *et al.* reported that children with asthma are at an increased risk of developing dental erosion as medications used to treat asthma can reduce salivary protection against extrinsic or intrinsic acids. There can be an increase in incidence of dry mouth in asthmatics due to the effects of mouth breathing which leads to increase in the consumption of drinks with a low pH and high titratable acidity to compensate oral dehydration which may result in dental erosion.¹⁰

There is evidence that medicines taken by dry powder inhaler may cause tooth erosion by changing the chemical environment of the mouth. Increased incidence of gastroesophageal reflux disease may also be responsible for dental erosion in asthmatic individuals. Medications used to treat asthma may also be one of the factors that promote gastroesophageal reflux development.¹²

Asthma and Periodontal Disease

The association between asthma and periodontal disease can be both attributed to the side effects of asthma medications and explained by the pathological activation of the immune and inflammatory mechanisms triggered by asthma. Hyypa indicated that gingivitis in asthmatic children develops due to an altered immune response as well as dehydration of the alveolar mucosa related with mouth breathing. Hanania *et al.* in their study showed that regular use of conventional doses of inhaled corticosteroids (ICS) by patients with asthma can suppress the adrenal function and decrease bone density in a dose-related fashion. Systemic bone loss caused by these drugs, especially when high doses are used for a long time, may have an impact on the onset and progression of periodontal disease.¹⁰

Dysphonia

Dysphonia, or hoarseness, is a common adverse effect of ICS on larynx. It has been estimated to occur in 5 – 50% of patients using ICS. The extent of dysphonia is dependent on

vocal stress and ICS dose, and dyskinesia of muscles that control vocal cord tension. Steroid-induced myopathy affecting the vocal cord muscles may, in some cases, result in bilateral adductor fold deformity with bowing of the folds on phonation.¹³

Pharyngitis

Pharyngitis is one of the most common local side effects associated with currently available ICS. The incidence of pharyngitis ranges from 4 – 25%. Pharyngitis is generally accompanied with the symptoms of pain, irritation, or soreness in the throat. Dysphagia is common with pharyngitis, and throat pain is often aggravated by swallowing (odynophagia).¹³

Cough

Although bronchospasm and persistent cough are rare side effects of ICS, reflex cough during inhalation is common. Cough is most likely caused by an irritant effect of inhaled excipients in the ICS formulation (e.g. fluorocarbons or detergents) or from a nonspecific direct irritant effect of ICS.¹³

Recommendations for prevention of adverse effects

Persistent asthma can be effectively controlled with currently available ICS. Dental practitioner recommendations for asthmatic patients can be listed as follows:

- Asthmatic individuals are in the group of people who are in need for special care and, thereby, dental visit frequency can be increased
- Asthmatic children and their parents should be informed about the impacts of the asthma medications on oral health
- Patients should be informed that they should rinse their mouth thoroughly with mouthwashes with a neutral pH, or sodium bicarbonate, milk or neutral sodium fluoride containing solutions after the use of inhaler
- Measuring bone mineral density can be recommended for patients using inhaled corticosteroids
- A spacer can be added to the inhaler in order to decrease the deposition of the medication in the mouth.¹²

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