Role of Bronchodilators in Management of Cough

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Introduction

Cough is one of the commonest and distressing symptoms of lung disease and is a frequent problem encountered in general practice as well as hospital practice.

Cough is a reflex phenomenon occurring when sensitive receptors located in the larynx and upper airways are activated.

These receptors generate information which reaches the central nervous system. The central organization of cough reflex loop is poorly understood. The afferent pathways originate in receptors situated under and between airway epithelial cells. Most are rapidly adapting receptors (RAR) linked to myelinated fibers of vagus nerve which can be directly stimulated by cough inducing agents other receptors generate information carried by non myelinated C fibers. When activated these receptors release neuro peptides leading to neurogenic inflammation which can also activate RARS. The threshold of the cough reflex and its expression this depends on a complex interaction between RARS and C fiber receptors with peripheral and central components.

Chronic cough is a major clinical problem. The causes of Chronic cough can be categorized in eosinophilic and non eosinophilic disorders. Former being comprised of asthma, cough variant asthma (CVA) atopic cough (AC) and nonasthmatic eosinophilic bronchitis (NAEB).

Cough is one of the major symptoms of asthma. Cough in asthma, can be classified into three categories (1) CVA asthma presenting solely with coughing (2) cough predominant asthma predominantly presenting with coughing but also with dyspnea and or wheezing and cough remaining after treatment with inhaled corticosteroids (ICS) and beta – 2 agonists in patients with classical asthma despite control of the other symptoms. There may be two subtypes. In the last category one is cough responsive to antimitediator drugs. Such as leukotriene receptors antagonists and histamine H1 receptor antagonists and then other is cough due to comorbid conditions such as gastrooerophageal reflux. CVA is of the one of the commonest causes of isolated cough. It shares a number of pathophysiological features with classical asthma with wheezing such as atopy airway inflammation and various features of airways modeling one third of adult patients may develop wheezing and progress to classical asthma.

Atopic cough presents with bronchodilator resistant dry cough associated with atopic constitution. It involves eosinophilic tracheo bronchitis and cough hypersensitivity and responds to ICS treatment, while lacking AHR and variable airflow obstruction. This features are showed by non asthmatic eosinophilic bronchitis (NAEB) however atopic cough does not involve bronchoalveolar eosinophilia and has no evidence of airway remodeling and rarely progresses to classical asthma unlike CVA and NAEB Histamine H, antagonists are effective in atopic cough but their efficacy in NAEB is unknown AHR of NAEB may improve with ICS within normal range. Taken together NAEB significantly overlaps with atopic cough but might also include milder cases of CVA with modest AHR. Many patients with persistent cough especially children are diagnosed as having asthma and are treated with asthma medications including inhaled corticosteroids and agonists. Recent ACCP American Association of chest physicians evidence based clinical practice guidelines affirm that patient with chronic cough asthma should be always be considered as potential etiology because it is common condition with which cough is commonly associated.

The Role of Inhaled Corticosteroids and Beta – 2 Agonists in Cough and Asthma

In an excellent review of management of chronic cough in adults. Morice and kastelik1 described three corticosteroid responsive cough syndromes, classical asthma, cough variant of asthma and eosinophilic bronchitis all characterized by sputum eosinophilia, although eosinophilic bronchitis is without bronchial hyperresponsiveness. In particular, in cough variant asthma, cough responsive to bronchodilator treatment can be the principal or only manifestation of asthma, especially in young children. Monitoring of PEF of bronchoprovocation may be helpful and, in any case, diagnosis is confirmed by a positive response to asthma medications. Morice and Kastelik1 have omitted atopic cough, a bronchodilator-resistant non-productive cough that has been defined as an isolated chronic cough with no variable airflow obstruction or airway hyperresponsiveness and one or more objective indication of atopy as identified by blood or sputum eosinophilia, elevated total or specific IgE or positive skin tests.2 Whether cough with sputum eosinophilia but without variable airflow obstruction and / or hyperresponsiveness is a form of asthma remains debatable.

The Role of Inhaled Corticosteroids

Inhaled Corticosteroids in Cough of Classical Asthma

As cough threshold in asthma can be related to the degree of the underlying airway inflammation, an inhaled corticosteroid can reduce cough symptom and cough threshold.3 A study, which has compared fluticasone propionate 50 µg twice daily and 100 µg twice daily with placebo in young asthmatic children, has documented that after 12 weeks of treatment, the effect of the inhaled corticosteroid was most clearly revealed by reduction in cough and use of salbutamol, with no significant differences between fluticasone 50 µg twice daily and 100 µg twice daily.

Unfortunately, the causes of cough in asthma may not only involve airway inflammation; increased secretion and / or decreased clearance of mucus may play a significant role as well.4 Passive smoking may also be a relevant factor; it may make children more vulnerable to viral infections5 (Becker and Soukup, 1999), and parents who smoke scores. These factors may mask any effects of inhaled corticosteroids and result in underestimation of symptoms. In any case, as highlighted by the recent ACCP evidence – based clinical practice guidelines (Boulet, 2006), smoking asthmatic patients, who account for about 25% of the asthmatic population, are a subgroup that requires attention because they have a reduced response to agents such as corticosteroids (Chalmers et. al. 2002). The lack of response to corticosteroids may be secondary to the increased...
Inhaled Corticosteroids in Cough Variant of Asthma

Corticosteroids are effective not only in cough of classical asthma but also in cough variant of asthma. Cough variant of asthma is common cause of isolated cough, accounting for around 30% of cough referrals to cough clinics (Pavord, 2004). Typically the cough is dry or minimally productive, it may occur nocturnally, after exercise or allergen exposure, although there are often no clinical clues. A recent study has documented that although the pattern of inflammatory sputum markers in patients with asthma and cough variant of asthma is similar, its relation with bronchial hyperreactivity and cough sensitivity is different in each group (De Diego et al. 2005). There were no significant differences in either the inflammatory pattern of soluble markers or differential cell counts between classic asthma and cough variant asthma. Histamine PC 20 was correlated with IL–5 in cough – variant asthma, whereas it was associated with sputum eosinophilia in classic asthma. Cough variant of asthma is particularly well recognized in children, although there is some evidence of over diagnosis (Fitch et al. 2000). Longitudinal studies have demonstrated that up to one-third of patients who present with cough variant asthma later develop the typical wheezing of classical asthma.  

A short course of prednisone (40 mg q.d. or equivalent for 1 week) as a diagnostic-therapeutic trial can establish a diagnosis and be followed by an effective method of control of cough by inhaled corticosteroids. As is usual in classical asthma, in fact, cough variant of asthma responds to treatment with inhaled corticosteroids. This treatment must be considered important because there is clear evidence that long-term inhaled corticosteroids significantly decreases the development of typical asthma in patients with cough variant of asthma. It must be noted that, in some patients with cough variant of asthma, cough may actually be exacerbated by inhaled corticosteroid therapy, as a result of a constituent of the aerosol. In such cases, a diagnostic therapeutic trial of oral corticosteroids (prednisone) is appropriate. 

The Role of B2 – Agonists

Although large amount of work has demonstrated that the underlying mechanisms of cough and bronchospasm are different (Forsberg et al. 1992; Karlsson et al. 1992) experimental studies indicate that airway caliber increases the sensitivity of the afferents involved in the cough reflex (Karission et al. 1992). This is an important finding, although it must be highlighted that this has proved difficult to demonstrate in humans. 

The large difference in potency of salbutamol in allergic- and capsaicin-induced cough is suggestive of different mechanisms of action of the drug in each model. Salbutamol may inhibit allergic cough by reducing release of provocative mediators from surface mucosal mast cells. Conversely, salbutamol may inhibit capsaicin-induced cough by reducing the responsiveness of C-fibers to capsaicin. The extent to which these different mechanisms account for the described observations regarding the potency of salbutamol is still unknown. However, Yagi et al. suggested that airway contractility affects the frequency of cough induction and, consequently, salbutamol is mainly active because of its capacity of inducing bronchodilator. 

It is possible that those with high bronchodilator response measurements would benefit. It must be highlighted that a systematic review by Smucny et al. has shown that there is no evidence to support using B 2-agonists in patients with acute cough and no evidence of airflow obstruction. Besides, Fujimura et al. documented the intriguing finding that there is atopic non-asthmatic bronchodilator resistive cough, which is a different entity from bronchodilator-responsive cough, or the so-called cough variant of asthma.

Conclusion

According to the latest ACCP evidence-based clinical practice guidelines for the diagnosis and management of cough, patients with cough due to asthma should initially be treated with a standard antiasthmatic regimen of inhaled bronchodilators (B 2 – agonists) and inhaled corticosteroids. For cough that is severe or only partially responsive to inhaled corticosteroids, oral therapy (i.e. prednisone 40 mg or equivalent daily for 1 week), alone or followed by inhaled therapy, may be necessary. However, the possibility of inhaled corticosteroid-induced cough, improper use of the inhaler device, or the presence of aetiology, such as gastroesophageal reflux disease, making asthma difficult to control, should be excluded before the escalation of therapy. In those patients in whom cough remains refractory to inhaled corticosteroids, an assessment of airways inflammation is helpful. The presence of airway eosinophilia demonstrated by the evaluation of induced sputum or BAL fluid will identify those patients who may benefit from more aggressive anti-inflammatory therapy (i.e. higher dose inhaled corticosteroids or oral steroid therapy) (Irwin et al. 2006). 

In any case, it must be highlighted that if the cough resolves with inhaled corticosteroid use, clinicians should still recognize that the patient does not necessarily have asthma, and he / she should be re-evaluated after asthma treatment has been stopped. The resolution of cough may occur with the period effect (i.e. spontaneous resolution) (Evald et al. 1989) or a transient response. Moreover, it cannot be omitted that the study of Chang et al. which was documented that salbutamol or beclomethasone has no effect on cough frequency or score, irrespective of the presence of airway hyperresponsiveness, questions the existence of cough variant of asthma. It also raises the appropriateness of the common practice of using either B 2-agonists or inhaled corticosteroids in the treatment of patients with cough without any other evidence of airway obstruction. 

References


