Future Drugs for the Treatment of Dry Cough

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Abstract

Cough is a commonly frequent debilitating symptom that is often viewed as an intractable problem. However, specialist cough clinics report very high success rate, in the order of 90%. The key to successful management is to establish a diagnosis and treat the cause. Idiopathic cough is rare and commonly misdiagnosed, because of the failure to recognize that cough is often caused from sites outside the airway. Asthma, gastric reflux and rhinitis are common causes from three different anatomical areas and the realms of different specialists.¹ This problem is complicated by the frequently atypical presentation of patients with cough. Thus, patients with cough-predominant asthma may not exhibit bronchoconstriction, and patients with reflux-associated cough may have no associated reflux symptoms such as heartburn.¹ Hence, this warrants a detailed history and evaluation to reach a diagnosis for successful treatment. The following article aims to provide a framework for a logical approach, for patients with this highly disabling symptom.

Introduction

Cough is a forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound¹. Cough is an important defensive reflex to protect the airway from chemical irritants and foreign body. Acute cough is defined as one lasting less than 3 weeks while chronic cough is defined as one lasting more than 8 weeks.²³ Persistent cough is a major cause of morbidity being reported by 10-20% of the population⁴ and 5th common symptom reporting to out patient clinics.⁴ Persistent cough may be associated with considerable morbidity including sleep loss, exhaustion, urinary stress incontinence, cough syncope and socioeconomic burden due to work absenteeism.⁵⁶ Some of the more serious side effects of cough reported are rib fractures, pneumothorax, pneumomediastinum, and subcutaneous emphysema.

The cough reflex is sub served by vagal efferent pathways arising from the trachea and intrapulmonary airways, and by the larynx whose afferent nerves pass into the superior laryngeal nerves. Cough-sensitive nerves in the lower airways extend to the division of segmental bronchi and possibly beyond. The most important tussigenic zones are at the level of the larynx and trachea, especially in the region around the carina. Sensory nerve fibers presumed to mediate cough are present in the airway epithelium and have been observed under the electron microscope.⁷ Cough receptors have also been described in the auditory canals which are sub served by the auricular branch of the vagus nerve. The afferent pathways are carried to the medulla in the brainstem. An abnormality of these central pathways in chronic persistent dry cough is a possibility. In disease states, excessive coughing can occur by excessive noxious stimulation of these afferent fibers and/or as a result of sensitization of neurons involved in the cough reflex. Patients with a nonproductive persistent cough have an enhanced cough reflex.¹

Common Causes of Dry Cough

Cough after an upper respiratory virus infection is transient.⁶ Persistent cough may have a variety of causes, as seen in the table and sometimes a combination of these.² Post-nasal drip is a symptom; with a differential diagnosis including, allergic rhinitis, vasomotor rhinitis, viral or bacterial infections, and nasal polyps. Patients complain of need to clear the throat frequently and a sensation of something at the back of the throat.² If suspected, a detailed ear, nose, throat (ENT) examination including nasal endoscopy is essential.¹ Nasal inflammation can be treated with topical corticosteroids. However, a considerable body of evidence supports the use of first generation sedating antihistamines in chronic cough, often in combination with sympathomimetic “decongestants”. Rarely patients with middle ear pathology present with cough due to irritation of the auricular branch of the vagal nerve (Table 1).

In a subgroup of asthmatics, cough is the predominant complaint; termed CVA, i.e. cough variant asthma. Typical symptoms and signs of asthma, such as wheeze, chest tightness may not be seen in CVA. Diurnal peak flow variability and nocturnal exacerbation is suggestive.⁴ Pulmonary function with methacholine challenge is the gold standard for the diagnosis and inhaled corticosteroids, as used in the management of asthma helps in controlling the cough.

Eosinophilic bronchitis (EB) is a recently recognized entity, presenting with chronic cough and sputum eosinophilia.⁵ EB is different from asthma, in the localization of mast cells within the airway wall. Airway smooth muscle infiltration occurs in patients with asthma and epithelial infiltration in patients with nonasthmatic eosinophilic bronchitis. Diagnosis is made by the confirmation of eosinophilic airway inflammation in induced sputum analysis after the exclusion of other causes for chronic cough. Patients do not demonstrate reversible airflow obstruction or hyperresponsiveness to methacholine. This type of cough usually responds well to inhaled corticosteroids, thereby probably causing many patients with this condition to

Table 1: Common causes of dry cough

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Non-respiratory</th>
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<tbody>
<tr>
<td>Post viral infections of the Upper respiratory tract</td>
<td>Gastro-esophageal reflux</td>
</tr>
<tr>
<td>Post nasal drip</td>
<td>Angiotensin converting enzyme-inhibitor (ACE) induced</td>
</tr>
<tr>
<td>Cough variant asthma</td>
<td>Psychological</td>
</tr>
<tr>
<td>Eosinophilic Bronchitis</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Mediastinal tumours</td>
<td></td>
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<tr>
<td>Pleural diseases</td>
<td></td>
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<tr>
<td>Early interstitial fibrosis</td>
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be misdiagnosed with CVA. The dose and duration of treatment differ between patients. The condition can be transient, episodic, or persistent unless treated, and occasionally patients may require long-term prednisone treatment. In a recent prospective study, EB was shown to be the cause of chronic cough in 13% of patients referred. Whether EB represents a distinct clinical entity or shares a pathophysiological spectrum with CVA remains to be clarified.

Cough is the predominant symptom in conditions affecting the pleura, mediastinum and interstitium along with symptoms such as fever, weight loss or dyspnoea. These conditions need to be evaluated as per history, signs and the chest radiograph.

Gastro esophageal reflux (GER), affects 4-21% of adult population, may be suggested by the presence of classic symptoms such as dyspepsia, heartburn, or water brash. Hoarse voice, aphonia, laryngitis, asthma, cough, chest pain, and dental erosions are symptoms being increasingly recognized. GER reflux is usually caused by transient relaxation of the low esophageal sphincter (LES). Thus, cough may occur after meals, while eating, when supine or bending. Cough usually diminishes during sleep as the LES closes and recurs on adopting an upright posture. Injuries to the mucosa and vagally mediated mechanisms by which reflux-related extra-esophageal tissue injuries occur may occur. Talking or laughing precipitates reflux cough since the diaphragm is an important component of the LES.

Continuous monitoring of tracheal and esophageal pH and esophageal manometry, (the diagnostic tools for GER), has demonstrated significant falls in tracheal pH (down to 4) during these episodes of reflux.

Angiotensin-converting enzyme (ACE) inhibitors are often prescribed for the treatment of hypertension and cardiac failure. The estimated frequency of ACEi-induced dry cough is 15%. One hypothesis is that ACE inhibitors prevent the degradation of endogenous kinins such as bradykinin, and allows bradykinin to sensitize the cough receptors directly or through the release of prostaglandins.

The etiology of cough cannot be identified in 78-99% of patients attending a specialized clinic. For patients with idiopathic persistent dry cough, specific treatment of the underlying cause is, impossible and treatment must rely on antitussive therapy. Cough sensitivity to inhaled tussigens such as capsaicin is also enhanced in these patients, and it is tempting to suggest that an ideal antitussive drug would reduce this altered sensitivity to normal, without significant adverse effects. Despite significant advances in our understanding of the pathogenesis of cough, such a drug is not yet available.

### Evaluating a Case of Dry Cough

A detailed history is vital in a patient with persistent dry cough. Initial investigations necessary to obtain are a plain chest radiograph and a spirometry (flow/volume loop) with bronchodilator reversibility. Alternatively diurnal measurement of peak flow readings at home may show a significant variability also suggesting asthma (Figure 1).

In presence of an abnormal chest radiograph, further investigations are warranted based on the history and radiographic features. These usually include computed tomography (CT) thorax, and flexible fiberoptic bronchoscopy (FOB).

A trial with either inhaled steroids/bronchodilators in CVA or nasal steroids with antihistamines in post-nasal drip or proton pump inhibitors in GER are merited in patients with a possible diagnosis of the conditions. However, if patients continue to be symptomatic despite treatment for optimum duration then more specific investigations are required like bronchoprovocation with histamine or methacholine for CVA, 24 hour esophageal pH monitoring for GER, and combined formal ENT assessment/CT sinuses in suspected post-nasal drip. Demonstration of bronchial hyperresponsiveness (BHR) by methacholine inhalation challenge (MIC) testing is regarded as the diagnostic gold standard for CVA, it is important to know that a positive MIC is merely consistent with, not diagnostic of, CVA. A confirmation is achieved only when there is a complete resolution of cough, which is usually within a week of initiation of inhaler therapy. However treatment may be required for up to 8 weeks. In patients with partial response to inhaler or in severe cases a trial of short course of oral steroids followed by inhaler may be tried. Recent studies suggest that leukotriene-receptor antagonists may be particularly effective in treating CVA.

Monteleukast / Zafirlukast for a fortnight, has been shown to...
improve cough, and to inhibit objectively measured cough reflex sensitivity in patients with CVA, including a subgroup whose cough had been refractory to inhaled steroids.2,3,6

Several investigational techniques may be used to diagnose gastro esophageal reflux; however, because of the poor sensitivity of endoscopy and pH monitoring, and the poor specificity of laryngoscopy, empiric therapy with proton-pump inhibitors (PPI) is now considered the initial diagnostic step in patients suspected of having GER-related symptoms.6 In those who are unresponsive to such therapy, other diagnostic testing such as impedance/pH monitoring may be advisable in order to exclude continued acid reflux. However, PPI-unresponsive patients usually have causes other than GER or a combination of other causes of cough. No clinical trial had been addressed to evaluate the effects of nonpharmacological interventions in reducing GER-induced cough. Patients seem to benefit from sleeping with an elevated head, smoking cessation, weight reduction, a diet rich in protein and low in fat, and in food and beverages that may relax the LES, such as alcohol, chocolate, mint, onion, coffee, tea, cola and citrus fruits. Combination of conservative and lifestyle measures with proton pump inhibitors and/or prokinetic agents for a period of 3 months resolves GER induced cough in 70–100% of patients, and increases the cough threshold in patients with reflux esophagitis.10,11 Failure of PPIs must be considered only after adequate dosage (omeprazole 40 mg twice daily) has been used for 12 weeks. Prokinetic agents exert their effects by increasing LES tone and facilitating gastric emptying. They are usually prescribed in association with PPIs. Anti-reflux surgery (open or laparoscopic fundoplication) is the treatment of choice for those patients with proven GER disease whose cough persists after 3 months of appropriate medical treatment, including high dosage of PPIs.11 Surgery is particularly indicated for patients who present with symptoms and signs of recurrent aspiration in the respiratory tract. Surgical therapy has been shown to be more effective in those patients with normal esophageal motility.

Successful management strategy for cough, based on cost effectiveness, points that treatment started after testing for every cause was most expensive and importantly shortest duration. In contrast, treating sequentially, starting with rhinitis was the cheapest option but had the longest treatment duration. Therefore, the challenge is to balance the cost with time to treatment success. Thus, in patients without asthma and postnasal drip, an empirical 2-week treatment trial of high-dose PPIs was more reliable than investigations such as manometry and pH testing. Twenty percent of patients with cough may present with more than one aggravating factor and this group of patients may need a more complex management regime before symptom resolution is achieved.2 Evidently, treatment options for cough are far from satisfactory, and have been described as an unmet need for the patient. Management of cough is highly variable in clinical practice, and some of the reasons for this may include the unsystematic evaluation of causes of cough and the frequent use of non-specific cough treatments.

Levodopropazine, Moguisteine and Levocloperastine are new peripherally acting antussives.12 Baclofen, Thalidomide, Gabapentin, Carbamazepine and Amitriptyline are experimental options that could have a role in the management of cough.13 Recent evidence suggests that calcitonin gene-related peptide (CGRP) and substance P (SP) may play a role in the pathogenesis of idiopathic persistent dry cough, and antagonists of these compounds may prove useful as potential antitussive treatment in future studies.14

Conclusions

It ought to be stressed that more than one of these conditions may coexist and cough may only respond with concomitant treatment of both (e.g. asthma with post-nasal drip). Often, symptoms of reflux, post-nasal drip or asthma are absent, and a ‘blind’ therapeutic trial of medication specific for these conditions may be indicated. However, it would be preferable to proceed to investigations first. Patients presenting with persistent dry cough are best served by thorough investigation, particularly for asthma, GER, and post-nasal drip. There is an urgent need for more high quality research to build the evidence base around the management of cough in respiratory illness, more attention from the physicians and higher investment from the industry. Efficacy of cough suppressants must be tested in double-blind randomized trials using validated measures of cough in patients with chronic cough not responding to specific treatments.

References

8. Ing AJ, Ngu MC, Breslin ABX. Chronic persistent cough and gastroesophageal reflux.