Role of Mucolytics in Wet Cough

Raja Dhar*

Mucolytics or ‘cough syrup’ constitute the most common medication used by a respiratory physician in India. In this class, expectorants comprise the lions’ share of a general physician’s prescription. This class of medication acts by reducing the irritation of cough receptors due to mucous accumulation and by coughing up of this mucous. The sequelae of mucous hypersecretion is airway obstruction, air flow limitation, ventilation perfusion mismatch, and impairment of gas exchange.1,2 The secretion is airway obstruction, air flow limitation, ventilation perfusion mismatch, and impairment of gas exchange.1,2 The spectrum of diseases in which there is excessive sputum production due to airway mucous hypersecretion include asthma, chronic obstructive pulmonary disease (COPD) or cystic fibrosis (CF). Slowing or paralysis of the mucociliary escalator will reduce mucous clearance and increase bacterial colonization leading to repeated lower respiratory tract infection and exacerbations of airways disease.3-6 The issue of mucous hypersecretion is however more relevant to COPD and its role in asthma and CF is less well defined. It is hypothesized that in asthma excess mucous not only causes airway plugging but also contributes to bronchial hyper-responsiveness.3,5 Researchers have further contemplated that chronic mucous hyper-secretion reflects lack of asthma control leading in turn to accelerated loss of lung function and increased mortality. In summary, this results in airway obstruction, bacterial colonization and repeated infections and exacerbation.

This mucous hypersecretion is a reflection of the inflammatory process which is related to asthma, CF and COPD. Hence, it would be important to develop drugs that address the airway mucous problem in these patients. The inflammatory processes in these diseases results not only in the loss of respiratory function, but also in the destruction of the surfactant layer by airway phospholipases and by altering the biophysical properties of mucous. The byproducts which accumulate as a result of this inflammatory cascade includes neutrophil derived DNA and filamentous acts (F-actin), dead or apoptotic cells, bacteria and cellular debris.7 All these factors together contribute to mucous purulence and the material expectorated is termed as sputum. Drugs that are designed to specifically alter the viscoelastic properties of mucous in addition to promoting clearance of sputum are called “mucoactive”.

Mucoactive drugs can hence be classified as expectorants mucoregulators, mucolytic or mucokinetics based on their potential mechanism of action.

Mucolytics

Mucolytic can be classified into 2 categories “classic” mucolytics depolymerise mucin glycoproteins and “peptides” mucolytics: depolymerize DNA and F-actin polymer networks.

Classic mucolytics: The prototype agent in this group is N-acetyl cysteine (NAC) which in addition to being a mucolytic agent also has significant antioxidant and anti-inflammatory properties. Nebulized NAC when administered as an aerosol dissociates mucin disulphide bonds and other disulphide bond crossed linked gel component to reduce viscosity. Due to its antioxidant effect this agent can also protect against free radical damage,7,8,11 NAC decreased airway inflammation by reducing lysozyme and lactoferrin concentrations in smokers,12 inhibiting neutrophils and monocytes chemotaxis and oxidative burst responses in vitro,13 reducing the activation and number of neutrophils and macrophages in bronchoalveolar lavage and smokers,14,15 and by inhibiting the adherence of bacteria to ciliated epithelial cells in vitro.16 There is good evidence of prove that oral NAC has stabilized disease in idiopathic pulmonary fibrosis and may also reduce exacerbation rates in chronic bronchitis.17,18

Other Mucolytics: Erdosteine and fudosteine: Erdosteine is an antioxidant with mucolytic properties and also reduces bacterial adhesiveness. A small randomized controlled trial showed fewer exacerbations, reduced hospitalization time and improved quality of life in patients with COPD that were treated with erdosteine when compared with placebo;19 however, future trials will be necessary to confirm these findings. Fudosteine is a cysteine with greater bio-availability than NAC. It reduces hypersecretion by down regulation of mucin gene expression.

Peptide Mucolytic: These bring down highly polymerized F-actin network that is characteristic of pus. Dornase alpha is a proteolytic enzyme that cleaves DNA polymers and is used in the long term treatment of mucous hypersecretion in CF.20 Dornase α is used in children with CF with corresponding improvement in lung function and outcome.21 However these agents need to be evaluated further in clinical trial.

Non Destructive Mucolytic: These agents disrupt polyionic oligosaccharide mucin network by a mechanism termed “charge-shielding”. Dextran and heparin belong to this class. Preclinical
studies have demonstrated their efficacy. Larger clinical studies are however still to be undertaken.

Current Recommendations for Clinical Use of Mucolytic Drugs

Even though there is abundance of mucoactive drugs which are available only a few are recommended for use in respiratory hypersecretory disease. For e.g. even though the National Institute of Clinical Excellence (NICE) in the UK recommends mucolytic therapy in the management of COPD, most guidelines do not recommend this form of treatment. Neither the BTS nor the European Respiratory Society currently recommends mucolytic drugs in treatment. In Canada mucolitics are listed as one of a number of treatments “under investigations” and are not specifically recommended in disease management. The American Thoracic Society recommends mucokinetic agents “step 3” as an adjunct to bronchodilators when there is mild-to-moderate symptoms and also in severe exacerbations if the sputum is very “viscous”. As far as asthma guidelines are concerned, the BTS does not mention mucolitics at all and the American Thoracic Society also makes no such recommendations regarding mucolitics or expectorants.

Theoretical Requirements for Effective Therapy of Airway Mucus Hypersecretion: An agent which induces discharge or expulsion of mucus from the respiratory tract is called an expectorant. To facilitate this it typically requires the coughing and sneezing action which loosens the mucous from the lungs or the upper respiratory tract. These events can be thought to be protective because they might unplug obstructed large, medium or small airways. This might improve alveolar aeration and provide relief from neural irritation triggered by mechanical properties of mucous plug or effects of their inflammatory components. This will help in reducing the effort of breathing and improve dyspnoea. Some frequently used expectorants are discussed in summary below:

Hypertonic Saline

Aerosol using hypertonic saline (saline, urea, or ascorbic acid) has been thought to induce ciliary motility, proteolysis and mucous liquefaction. These agents promote the secretion of airway fluid. Even though these agents have long being used as expectorants their clinical use is controversial because of potential toxicity. Iodinated glycerol, first introduced in 1915, reduces chest discomfort and offers anti-tussive effects in patients with chronic bronchitis, without affecting dyspnoea or lung function. DMI increases secretion volume in adults with chronic bronchitis.

Guafenesin (Glyceryl Guaiacolate)

This may help to reduce bronchial sputum surface tension. It is mainly for symptomatic treatment of cough producing small quantities of thick viscous secretion. This agent has not been shown to be useful in randomized clinical trials.

Ion Channel Modifiers

Tricyclic nucleotides (uridine triphosphate and adenosine triphosphate) regulate ion transport through P2 Y2 purinergic receptors that increase intracellular calcium. Nebulized uridine triphosphate aerosol in the presence or absence of amiloride enhances mucociliary clearance in healthy subjects.

Mucoregulators

Agents that interfere with DNA /F-actin network to regulate mucous secretion are described as muco-regulatory agents. Their mechanism of action is wide ranging.

Carbocysteine is an antioxidant that has ability to restore the viscoelastic properties of mucous and provides anti-inflammatory effects, in addition to providing protective effects on respiratory cells. Carbocysteine is not thought to act directly upon the mucous structure but increases chloride transport across airway epithelium which might contribute towards its mucoregulatory action. The anti-inflammatory properties of Carbocysteine is by reduction of neutrophil infiltration into the airway lumen, decreased levels of interleukin (IL 8, IL 6) and cytokine levels exhaled in chronic obstructive pulmonary disease. It has been shown to be an effective and safe drug for the treatment of COPD in randomized clinical trials, reducing the incidence of exacerbations and improving quality of life. It should however be noted that in the PEACE (Preventive Effect of ACute Exacerbation) study that subjects were Chinese (25% non smokers) who had limited access to other drugs that target exacerbation (e.g. long acting bronchodilators and corticosteroids). Moreover, Carbocysteine has been shown to improve oxidative stress and chronic inflammation associated with severe chronic diseases in particular advanced cancer and cancer related syndrome both alone and in combination with other anti oxidant drugs.

Anticholinergic Agents

Anticholinergic medications reduce glandular output and sputum volume. This secretory response is mediated via M3 muscarinic receptors expressed on sub-mucosal airway cells. The various agents include atropine, ipratropium, scopolamine, glycopyrrolate and tiotropium. Atropine blocks mucociliary clearance of gel, but not the mucous sol phase. In contrast, ipratropium bromide does not appear to effect mucociliary transport.

Glucocorticoids

These are potent anti inflammatory agents used in the management of acute exacerbation of asthma and COPD. They have a definite influence on mucociliary clearance.

Macrolide Antibiotics

These have been used to treat a wide range of chronic inflammatory lung disorders. These agents include Azithromycin, Clarithromycin and Erythromycin. They are thought to be standard care therapy for CF bronchiectasis and most recently COPD. These agents reduce sputum productions in severe purulent bronchitis, diffuse pan-bronchiolitis, sinobronchial syndrome and otitis. Their long term safety in the treatment of COPD especially on grounds of breeding resistance to these antibiotics still needs to be addressed.
Mucokinetics

These agents act on cilia and increase mucociliary clearance. Mucokinetic medication includes bronchodilators, tricyclic nucleotides and ambroxol. Surfactants also promote cough clearance of mucous by decreasing the surface adhesion between mucous and airway epithelium. There is dispute regarding the activity of β₂ adrenergic agonists on mucociliary clearance. Some reports have shown that salmeterol could restore secretory functions in CF airway sub-mucosal glands serous cells, and that β₂ adrenergic agonists can enhance mucociliary clearance in patients with airway reversibility.

Ambroxol

This agent is thought to stimulate surfactant and mucous secretion, yet promoting normalization of mucous viscosity in viscid secretions. A recent systematic review towards evidence of generalized benefit using ambroxol for a range of parameters including secretolytic activity (promoting mucous clearance), anti inflammatory and anti oxidant activity and exerts local anesthetic effect.

<table>
<thead>
<tr>
<th>Mucoactive drugs and their potential mechanisms of action</th>
<th>Potential mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectorants: Hypertonic saline Guaifenesin</td>
<td>Increases secretion volume and/or hydration Stimulates secretion and reduces mucus viscosity</td>
</tr>
<tr>
<td>Mucoregulators: Carbocysteine Anticholinergic agents Glucocorticoids Macrolide antibiotics</td>
<td>Metabolism of mucus producing cells, antioxidant and anti-inflammatory effects, modulates mucus production Decreases secretion volume Reduces airway inflammation and mucin secretion Reduces airway inflammation and mucin secretion</td>
</tr>
<tr>
<td>Mucolytics: N-Acetylcysteine N-Acystelyn Erdosteine Domase alfa Gelsolin Thymosin β4 Dextran Heparin</td>
<td>Breaks disulphide bonds linking mucin polymers Antioxidant and anti-inflammatory effects Increases chloride secretion and breaks disulphide bonds Modulates mucus production and increases mucociliary transport Hydrolyses the DNA in mucus and reduces viscosity in the lungs Severs actin filament cross-links Severs actin filament cross-links Breaks hydrogen bonds and increases secretion hydration Breaks both hydrogen and ionic bonds</td>
</tr>
<tr>
<td>Mucoactive Drugs in Development</td>
<td></td>
</tr>
<tr>
<td>Surfactant</td>
<td></td>
</tr>
<tr>
<td>Thymosin β4</td>
<td></td>
</tr>
<tr>
<td>Dry powder mannitol</td>
<td></td>
</tr>
<tr>
<td>Denufosol tetrasodium (INS37217 respiratory) for cystic fibrosis</td>
<td></td>
</tr>
<tr>
<td>Erdosteine</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td></td>
</tr>
</tbody>
</table>

Use of MUO Active Agents as Over the Counter Medications (OTC) in Cough

Studies

i. Systematic review of randomized controlled trials of over the counter cough medications for acute cough in adults: 15 trials involving 2166 participants that all the inclusion criteria antihistamines seem to be no better then placebo. There was conflicting evidence on effectiveness of antitussives, expectorants, antihistamine – decongestant, and other drug combinations compared with placebo. The effect size was small and hence of doubtful clinical significance. The results should be interpreted cautiously.

ii. Over the counter (OTC) medications for acute cough in children and adults in the ambulatory setting. 26 trials involving 4031 patients were included. In children studies antitussives, antihistamines, antihistamine decongestants and antitussives bronchodilators combinations were no more effective than placebo. The result of one trial favored active treatment of mucolytics over the placebo. One trial tested two pediatric cough syrups and both preparation showed a “satisfactory response” in 46% and in 56% of children compared to 21% of children in the placebo group. A minority of studies reported adverse effects described at a low incidence such as nausea, vomiting, headache and drowsiness. The authors concluded that there was no good evidence for or against the effectiveness of OTC medications and acute cough.

Conclusion

The review of available literature shows that expectorants, mucolytics, and mucokinetic agents are unlikely to play anything other than a relatively minor role in symptom relief, reduction in exacerbations, or disease modification in asthma, COPD or CF. In CF, the defect is in CF transmembrane-conductance regulator. This will not be addressed by mucolytic therapy.

COPD is caused by cigarette smoking or due to exposure to biomass fuel. Smoking cessation is the only intervention shown to slow the decline in lung function. Many COPD patients are asymptomatic until late in their condition, by which time they may have lost the greater proportion of their lung function. Like most interventions in COPD, the introduction of mucokinetic agents at this late stage is unlikely to influence the natural course of illness. Introduction of mucolytic therapy at such a late stage is unlikely to significantly affect the decline in lung function.

Similarly, in asthma, inhaled corticosteroids and β₂ agonists are highly effective in improving symptoms and reducing risk of death.

The question that arises is whether the finding of a statistically significant effect of medication on mucociliary clearance or cough clearance is of clinical relevance. Do we increase the risk of Pneumonia by administering a drug which reduces mucus
transport? On the flip side, does the administration of a drug which promotes mucus clearance prevent pulmonary infections and slow down the deterioration of lung function? Different factors, such as the frequency of infective exacerbations, the changes in lung function, the experience of dyspnoea and the ease of expectation, are studied. Further research, however, is needed to establish more precisely the clinical benefit of a specific agent in patients and to examine the exact relationship between alterations in mucus transport induced by a certain drug and its clinical impact on patients.

References


