Mucolytics in COPD: Like red wine?

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Chronic obstructive pulmonary disease (COPD) has become a world epidemic, with its prevalence increasing worldwide. It is currently the fourth leading cause of death in the USA, and it has been estimated that it will become the third leading cause of death in the world by the year 2020[1]. A variety of oxidants and free radicals provoke an imbalance between oxidants and antioxidants in the lung epithelium and systemic circulation of smokers and patients with COPD. Decrease in the oxidative burden in COPD may be achieved by either decreasing the generation of oxidants or enhancing the antioxidant defenses. A decrease in oxidant generation can be achieved by avoidance of noxious gas particles, mainly by cessation of smoking. On the other hand, the augmentation of antioxidant defenses can be accomplished by either increasing the endogenous antioxidant enzyme products or enhancing the non-enzymatic defenses through the exogenous administration of antioxidant supplements[2]. Mucus hypersecretion is considered to be a major inflammatory manifestation of COPD. Apart from its inflammatory role, mucus hypersecretion is known to be associated with various indices of disease severity, including loss of lung function and the rate of hospitalizations, and with mortality[3]. Resveratrol is a component of red wine extract which has anti-oxidant properties and inhibits macrophage related inflammation in patients with COPD[4].

Mucoactive drugs, mucolytics and/or mucoregulators, have two main targets, namely decrease of the mucus hypersecretion and alteration in the oxidant/antioxidant balance[2,5]. Despite the widespread use of mucoactive drugs in COPD, the current evidence is not very supportive of their effectiveness. For this reason, the most recent GOLD report categorizes these drugs as "other possible treatments" in group D. This recommendation is based mainly on the fact that these drugs have been evaluated mainly in short term studies, and in a few long-term studies with conflicting results[6]. There are still many questions that need answering: Do we use the optimal dose? Are these drugs suitable for patients with frequent exacerbations? Should we use them only in the predominantly bronchitic phenotype? These questions need definite answers for us to decide whether or not to continue the widespread use of these drugs in our everyday clinical practice. Another critical point is the way in which we look at their possible beneficial effects. It appears that we have generally avoided performing well-designed long-term studies and that the published studies have focused mainly on parameters and biomarkers with low validity and/or low expectancy. What are we looking for by investigating the association of FEV_1 and the use of

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mucolytics? Is it reasonable, for example, to design a study with main outcome the effect of N-acetylcysteine (NAC) on FEV_1? If we consider that even successful bronchodilators such as tiotropium failed to alter the rate of decline of FEV_1 then perhaps it is not really reasonable to focus on such parameters.

Carbocysteine is a mucoregulator drug which acts on the metabolism of mucus producing cells and also by exerting antioxidant and anti-inflammatory effects. NAC is a mucolytic drug which acts both by breaking disulphide bonds linking mucin polymers, and simultaneously by altering the imbalance of oxidants and antioxidants through its antioxidant effects. The antioxidant effects are attributed mainly to its actions as a precursor of reduced glutathione and as a direct reactive oxygen species scavenger. If we analyze the evidence derived from clinical studies using either NAC or carbocysteine we might speculate that both these drugs provide effective options for reducing the exacerbation rate in patients with COPD[2,7,8]. Randomized trials and real life studies both document a beneficial effect of mucoactive drugs on the rate of exacerbations related to COPD and a preventive effect on the re-admission rate. We prefer not to comment on studies evaluating the anti-inflammatory action of mucoactive drugs. It is obvious that the inflammatory process in COPD is resistant to the majority of the currently available pharmaceutical preparations and particularly to single agents, since its multifactorial origin renders it difficult to control. Despite the evidence of their beneficial effect on exacerbations, which currently are considered a crucial parameter in the assessment of patients with COPD, mucoactive drugs are generally thought to be ineffective in COPD management. The whole issue needs further clarification from multiple viewpoints. The first study that evaluated the effect of a mucolytic drug on COPD exacerbations was the Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) study[9], a 3 year placebo-controlled, randomized trial of NAC given in a dose of 600 mg daily, involving more than 500 patients with COPD. The results of this study were considered negative on the primary outcome, since NAC failed to alter either the FEV_1 decline or the rate of exacerbations. In a sub-analysis, however, the study showed a positive effect (21% lower exacerbation rate) in patients not receiving inhaled corticosteroid treatment (ICS). This study provided a signal that NAC may significantly alter the rate of exacerbation in some patients with COPD. Another study which deserves attention is the placebo-controlled randomized one year study PEACE[7]. In this study, high doses of carbocysteine resulted in a significantly lower rate of exacerbations and significant improvement in the quality of life, although no effect on lung function testing was observed. Only a low number of study participants were on ICS. What is the secret that will make a difference to the outcome in studies of mucolytics in patients with COPD – the dose, the disease phenotype or the careful selection of study participants? The dose might be an easy explanation, since all this noise started from the IFIGENEIA trial[10], in which a dose of NAC triple that used in the BRONCUS study (i.e., 1,800 mg) was used for patients with idiopathic pulmonary fibrosis (IPF). But how many common pathways are there between COPD and IPF? How can we characterize an effect as beneficial when it fails to alter the natural course of a disease?

Two additional parameters: Phenotyping and the selection of patients. The first is a general term, but further attention reveals certain characteristics which might provide the ideal situation for the effects of NAC to be exerted. The BRONCUS and PEACE studies both showed that the use of ICS was not associated with positive effects of the mucoactive drugs. This might be attributed to the fact that mucoactive drugs have an effect on ciliated epithelial cells, an effect which might be lost when ICS are administered. The second issue is that of the underlying severity. The BRONCHUS study recruited patients with less severe COPD than those in the PEACE study. So, are patients with severe COPD the ideal group for mucoactive drugs? Finally the selection of patients for study of COPD is still restricted, and far from the real life situation. In the BRONCUS study patients with reversibility of airway obstruction were excluded. We might consider the above criterion as a bias since it excludes a significant percentage of our patients with COPD. So, in combination, the results of the two trials have given rise to a significant question: should we attempt early intervention with mucolytics, irrespective of ICS use, or should we use them only for the more severe forms of the disease? Is the combination with long-acting anticholinergics the ideal format, particularly if we consider the mucus regulatory role of anticholinergics? It is quite difficult to provide a definite answer to these questions, since the currently available study results do not support the relative efficacy of multiple treatments. A recently published one year placebo-controlled randomized study called HIASE[11] raised some further points while providing answers to others. In this study the dose of NAC was raised to 600 mg twice daily, the selection of patients was less restricted and the primary outcome was the evaluation of small airways using the forced oscillation

technique (FOT). The rate of exacerbations was evaluated as a secondary outcome. The NAC treated group showed beneficial results in both outcomes compared with the placebo group. It is of interest that in this study, which had a small sample size, the beneficial effects were observed irrespective of the use of ICS, in a cohort characterized by frequent exacerbations and studied according to the body mass index (BMI) and the presence of emphysema. Two major messages: the dose appears to play an important role, and the primary outcome is somewhat attractive if we consider the current theory on the pathophysiology of emphysema; that it starts from the small airways[12].

One study which attempted to clarify most of the above issues is the PANTHEON study[13]. PANTHEON is a prospective, ICS stratified, randomized, double-blind, placebo-controlled, parallel-group, multicentre trial designed to assess the efficacy and safety of high-dose (1,200 mg/daily) NAC treatment for one year in patients with moderate-to-severe COPD. The primary endpoint is the annual exacerbation rate and the secondary endpoints include the recurrent exacerbation hazard ratio, the time to first exacerbation, quality of life and pulmonary function. One particular feature of interest of the above study is the recruitment of non smoking subjects with COPD, since the study was conducted in China. The preliminary results[14] showed that NAC administration significantly affected the rate of exacerbations, and this effect was time dependent, indicating a continuous beneficial effect through the whole year. A significant interaction was observed between treatment and GOLD stage, with greater improvement with NAC treatment in the moderate GOLD subgroup (39% reduction) and in ICS-naïve patients. The drug was well tolerated. These were very provocative results, particularly concerning the exacerbation rate.

Have we reached the end of the road? Do we now have enough evidence to support the use of mucoactive drugs in our everyday clinical practice? Large industry-sponsored pharmacological trials have provided some evidence to indicate that our current treatment options might involve the use of mucoactive drugs at a higher dosage and for a specific group of patients (frequent exacerbators and possibly ICS naïve subjects). There is no evidence that this group of drugs might affect the serious outcomes such as mortality and disease progression. On the other hand, however, if we consider that the exacerbation rate is crucial for disease assessment, any possible beneficial influence on exacerbation may modify a significant feature of the disease progression. The most important message from the studies currently available with regard to mucoactive drugs appears now to be clearer than ever: we must treat our patients more aggressively, and we should try to phenotype them before initiating any mucoactive drug. We can now, therefore, definitely be more optimistic and more confident than ever with regard to the use of mucoactive drugs. The results of the PANTHEON study are encouraging and might offer our patients a better chance. We still need to identify those patients who will benefit the most from mucolytic/antioxidant drugs and to standardize the dose that will provide optimal effectiveness, and this will require larger trials to provide the relevant evidence. We still need to improve our skills in identifying and treating patients with COPD early in the course of the disease, and in convincing them to adhere to their medication for life, just like all the other patients with chronic diseases. Given the fact that we are not expecting any novel therapeutic agents in the near future, this target, along with the appropriate management of comorbidities, may represent the landmark of a new beginning for COPD in the next decade. In addition, we should keep in mind that mucoactive/antioxidant drugs share two properties with red wine: they may share possible common mechanisms of action, and they may get better with time! Enjoy…

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