Role of mucolytics in the management of COPD

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Abstract: There is, to date, no medical therapy that modifies the decline in lung function that occurs in COPD. As the disease becomes more severe, exacerbations of COPD become increasingly common, affecting patient quality of life and increasing health care costs. Mucolytic agents, through their actions on inflammatory and oxidative pathways, have potential benefits in COPD. This paper reviews the randomized controlled trial (RCT) evidence for the effectiveness of at least 2 months of daily therapy with oral mucolytics in COPD. Based on evidence from 26 RCTs, mucolytics reduce exacerbations by up to 0.8 exacerbations per year, with a greater effect in patients with more severe COPD. This effect appears to be of a similar magnitude to the reduction in exacerbations seen with tiotropium and inhaled corticosteroids (ICS), but RCTs that compared the agents would be required to confirm this. Mucolytics do not affect the rate of lung function decline, but they do not have any significant adverse effects. Mucolytic treatment should be considered in: patients with more severe COPD who have frequent or prolonged exacerbations; those who are repeatedly admitted to hospital; or in those patients with frequent exacerbations who are unable to take tiotropium or ICS.
Keywords: mucolytic, exacerbation, COPD, lung function, tiotropium

Interest is increasingly being directed at finding therapies that reduce the frequency and severity of COPD exacerbations and, in so doing, relieve associated morbidity and reduce health care expenditure (Friedman and Hilleman 2001).

Medicines in the class broadly defined as "mucolytics" are agents that have long been used in mainland Europe for chronic bronchitis (CB) and COPD, yet they are seldom used in other parts of the world including Australia and New Zealand. Potentially useful mechanisms of action of mucolytics in COPD include: thinning or regulation of production of mucus, promotion of mucociliary clearance and expectoration, and antioxidant or antibacterial activity. The reader is referred to detailed accounts of mucus pathophysiology and the pharmacology of mucoactive drugs (Rogers 2002), and the relevance of the antioxidant properties of N-acetylcysteine (NAC) in COPD (Dekhuijzen 2004).

Cochrane systematic review

A Cochrane systematic review evaluating the clinical effects of treatment with mucolytic agents in patients was first reported in 1999 and updated in 2001 and 2003 (Poole and Black 2003). To be eligible for inclusion in this review, studies had to be randomized, double-blind, placebo-controlled studies of oral mucolytics administered regularly for a period of at least 2 months to adults with COPD or CB. The primary outcomes were the number of exacerbations, and days sick or on antibiotics. Secondary outcomes were lung function and adverse events.

Extensive searching on 3 occasions identified 27 eligible studies, but 4 of these did not have information on the primary outcomes. The remaining 23 studies were

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included in the review. Subjects in the 21 earlier studies had CB, which was most often defined as having cough productive of sputum on most days for a minimum of 3 months for at least 2 consecutive years (Fletcher and Pride 1984). In the other 2 studies, subjects had COPD, a disease that is now defined by expert panels in the Global Initiative for Obstructive Lung Disease (GOLD) workshops as "a disease state characterized by airflow limitation that is not fully reversible. It is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles and gases". (Pauwels et al 2001). It is likely that most of the subjects with CB in the earlier studies also had COPD as most were smokers and, when lung function was measured, there was evidence of airway obstruction. In 12 of the studies the mucolytic used was NAC. Other study treatments were ambroxol (2), carbocysteine (2), sobrerol, carbocysteine sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC), and myrtol. Ten of the studies were conducted in Italy, 3 each in Scandinavia and Germany, 4 in the UK, 2 in several European countries, and 1 in the US. Six of the studies had a duration of less than 3 months. All of the 23 randomized controlled trials (RCTs) had a Jadad quality score of at least 2 out of 5 and 20 had a score of 3 or more (Moher et al 1996).

Meta-analysis of the included trials produced the finding of a small but statistically significant effect of mucolytics on exacerbation rates of 0.066 exacerbations per month (95% confidence interval [CI] – 0.054 to – 0.077). The annualized exacerbation rate of 2.7 per patient per year in the control group would thus be reduced by 0.79 exacerbations per patient per year with mucolytic treatment, which equates to a 29% reduction. Even though this approach will overestimate the number of exacerbations per year since more exacerbations occur during the winter months when the studies were performed, a reduction of 0.8 exacerbations per year would be clinically important. Evidence from the 2 studies with more severe subjects (mean FEV_1 of less than 50% of predicted) showed a reduction in the exacerbation rate of 0.13 per patient per month (1.56 per year), which is double that seen when all the studies were pooled. NAC is the mucolytic that has been most extensively studied; however, other mucolytics as a group had similar effects on exacerbation rates.

In the meta-analysis of studies in the Cochrane review, subjects who received mucolytic therapy were twice as likely to remain exacerbation-free in the study period (odds ratio [OR] 2.22, 95% CI 1.93 to 2.54) than if they had received placebo. The number needed to treat (NNT) for 3–6 months to achieve 1 less exacerbation over that time was 6. Treatment with mucolytics resulted in 0.56 days less of disability per patient per month (95% CI – 0.77 to – 0.35). This finding was based on a smaller number of studies (6) but was supported by 4 other studies where mean values were reported without standard deviations. All 4 studies showed a reduction in days of disability with mucolytics of between 0.3 and 3.9 days per patient per month. A similar-sized effect was seen for days on antibiotics as well. These findings suggest that the exacerbations that do occur while taking mucolytics are less serious or less prolonged.

The findings in the Cochane review are supported by 2 other systematic reviews of the effects of NAC in CB. The larger of these included 11 RCTs (Stey et al 2000). Overall, those treated with NAC were more likely to remain exacerbation-free (OR 1.56, 95% CI 1.37 to 1.77), with a NNT of 5.8 (95% CI 4.5 to 8.1). Subjects were more likely to report an improvement in symptoms with NAC (OR 1.78, 95% CI 1.54 to 2.05) than with placebo. The second review (Grandjean et al 2000b) analyzed 9 trials that had been included in both the Stey and the Cochrane review and confirmed the significant effect on exacerbations (standardized mean difference – 1.37, 95% CI – 1.5 to – 1.25).

For the periods of the studies included in the Cochrane review (2–24 months), there was, however, no convincing evidence of any beneficial effect of mucolytic agents on lung function.

The Cochrane review concluded that treatment with mucolytics produced a small reduction in exacerbations and a somewhat greater reduction in the total number of days of disability in a population of patients with CB or relatively mild COPD. It was felt that a value judgement of physician and patient was required as to whether the benefits were sufficient to warrant the routine use of regular mucolytics in these patients.

The reviewers called for future studies to address the value of mucolytic therapy in patients who had 4 or more exacerbations a year or who have prolonged or severe exacerbations or repeated admissions to hospital with exacerbations of COPD.

The Cochane review is currently undergoing a further update to take account of recent new studies of mucolytics in COPD (Malerba et al 2004; Moretti et al 2004; Decramer et al 2005).

Recent RCTs of mucolytics

The findings of a 3-year RCT of NAC 600 mg per day vs placebo in 523 subjects with COPD have been keenly awaited (Decramer et al 2005). This rigorously conducted study took place in 50 European centers across 10 countries. The primary endpoints related to yearly decrease in lung function, and secondary endpoints to quality of life and cost utility. The study included men and women from 40 to 75 years, with a mean age of 62 years. All had smoking-related COPD, with an FEV_1/VC ratio of less than 88% in men and 89% in women, and minimal reversibility in FEV_1. The mean FEV_1 was 1.65 L (57% predicted) and mean reversibility with bronchodilator, 4%. Subjects had, on average, 2.5 exacerbations in the previous 2 years, with all having had at least 2. Subjects were stratified by concomitant use of inhaled corticosteroids (ICS), and by disease severity.

Over the 3-year period, there was no significant difference in the rate of decline of FEV_1 between the treatment and the placebo groups. This observation held regardless of underlying disease severity, and whether or not concomitant ICS were used. Overall, there was no significant difference in the annual exacerbation rates between the NAC and the placebo groups; however, when this was analyzed for the 155 subjects not taking ICS, there was a significant benefit of NAC over placebo, with respective rates of 0.96 per year vs 1.29 per year ($p = 0.040$). Subjects not on ICS had fewer moderate or severe exacerbations with mucolytic therapy than with placebo ($p = 0.032$).

A multicenter RCT using ambroxol 75 mg or placebo for 1 year in 242 patients with COPD also evaluated the effect on exacerbations (Malerba et al 2004). Concomitant use of ICS was forbidden in this study. The mean age of the subjects was 61 years and they had a mean FEV_1 of 2.1 L. Subjects had had a mean of 2.7 exacerbations in the past year. This study showed no overall difference in the number of subjects who were exacerbation-free in the 2 groups, although there were fewer exacerbations in total in the ambroxol treated group than in the placebo group (79 vs 103). Post hoc analysis showed that subjects with more severe symptoms who were treated with ambroxol were more likely to be exacerbation-free ($p = 0.038$) through the study period.

A third RCT studied the effect of 300 mg twice daily of erdosteine, a synthetic thiol compound with effects on bacterial adhesiveness, and with antioxidant and mucolytic properties (Moretti et al 2004). Investigators in 9 Italian centers enrolled a total of 155 subjects with COPD. 124 subjects completed the 8-month trial. The investigators permitted concomitant ICS therapy but did not report on the number of subjects using this therapy. Subjects had a mean age of 67 years, were predominantly male, and had mean FEV_1 of 59% predicted. The study is the only large study to show a beneficial effect of a mucolytic on lung function decline with a reported difference of around 300 ml between the 2 groups at the end of the study ($p < 0.01$). Erdosteine treatment was associated with greater likelihood of being exacerbation-free and fewer exacerbations than placebo treatment. Hospitalization rates were nearly halved in the erdosteine group. There were also statistically and clinically significant improvements in 6 minute walk distance and health-related quality of life scores.

Data from these 3 recent studies will inevitably result in a revision of the Cochrane review estimate of the effect size of mucolytic treatment on exacerbations in COPD. While the actual effect size is difficult to determine, and will vary depending on which studies are combined in meta-analysis, there seems to be consistency in the evidence in 3 main areas: (i) there is a significant and persisting effect of mucolytics as a group on the total number of exacerbations; (ii) regardless of the definition of COPD or CB, study subjects seem to experience between 2 and 3 exacerbations in the year prior to the study; (iii) those on mucolytics are more likely to be exacerbation-free during the study period.

Mode of action of mucolytics

How mucolytic agents reduce exacerbations is not yet clear. As a group they are heterogeneous in effects, and thus they may act at different points in the inflammatory and oxidative pathways that contribute to the development of COPD. The role of oxidants in the pathogenesis of COPD (Rahman and MacNee 1996) and exacerbations (Rahman et al 1997) is increasingly being recognized. Several of the agents studied in the Cochrane review (such as NAC, ambroxol, and carbocysteine) have antioxidant properties. However, there was a lack of an effect seen with NIC (a thiol donor derivative of NAC) on exacerbations or days sick (Ekberg-Jansson et al 1999). This finding argues against the actions of mucolytic agents as thiol donors being the most important mechanism in the reduction of exacerbations, although actions via other antioxidant mechanisms are not excluded. Prolonged treatment of COPD patients with 600 mg daily of NAC reduces the production of H_2O_2 (a biomarker of oxidative stress) compared with placebo (Kasielski and Nowak 2001).

In this study the effect on H_2O_2 exhalation was not seen until at least 9–12 months of treatment, yet beneficial effects of mucolytics on exacerbations have been seen in shorter studies lasting for 3–6 months, again suggesting alternative mechanisms. In another study treatment with NAC 600 mg twice daily for 2 months in patients with stable COPD resulted in a marked decline in breath H_2O_2 compared with placebo ($p = 0.003$) (De Benedetto et al 2005). This suggests that dose is important for any antioxidant effect.

Mucolytics may work through antimicrobial and/or immunostimulatory mechanisms. In CB, pretreatment with NAC resulted in significantly fewer patients having positive cultures from intrabronchial samples (Riise et al 1994). In COPD, long-term treatment with NAC has been shown to reduce the adhesion of neutrophils to cultured endothelial cells (van Overveld et al 2000) and to enhance macrophage-related killing of *Staphylococcus aureus* (Oddera et al 1994). A RCT found that 6 months of treatment with NAC in adults without chronic lung disease who had not received influenza vaccination, was associated with a significant decrease in incidence of influenza-like episodes than with placebo (29% vs 51%, $p = 0.0006$) (de Flora et al 1997). One of the few approaches that has been shown to reduce COPD hospital admissions is treatment with an immunostimulant bacterial extract, OM 85 BV, or bronchovaxom (Collet et al 1997).

Other agents have been shown to reduce exacerbations in COPD. The most convincing evidence of efficacy has been presented for tiotropium, a long-acting anticholinergic agent. The 2005 Cochrane systematic review of tiotropium in COPD included 9 RCTs, with a total of 6584 patients (Barr et al 2005). Meta-analysis showed that tiotropium reduced the odds of a COPD exacerbation (OR 0.74, 95% CI 0.66 to 0.83) and related hospitalization (OR 0.64, 95% CI 0.51 to 0.82) compared with placebo or ipratropium. The reviewers calculated that the number of patients needed to treat with tiotropium for 1 year to prevent 1 exacerbation was 14 (95% CI 11 to 22). Tiotropium also improved symptoms and quality of life, benefits that have not been shown with mucolytics.

The strongest evidence that the use of ICS reduces exacerbation frequency comes from the ISOLDE trial in which 751 men and women aged between 40 and 75 years with severe COPD (mean $FEV_1 < 50\%$ predicted normal) were treated with 500 µg fluticasone dipropionate twice daily for 3 years or placebo (Burge et al 2000). In the ICS-treated group exacerbations reduced from 1.32 per year to 0.99 per patient per year ($p = 0.026$), an absolute reduction of 0.33 exacerbations per year, or 25%. Subjects taking ICS also had a slower decline in health status than those in the placebo group. This finding has resulted in a Level A recommendation for the use of inhaled steroids in people with moderate or severe COPD and repeated exacerbations, in the latest GOLD guideline (Pauwels et al 2005). In the same document mucolytics as a group remain unsupported as effective therapy in COPD receiving a level D recommendation, although NAC receives a B level recommendation. While the B level recommendation seems justified on the strength of the evidence for NAC, the BRONCUS study findings might prompt some qualification of the support for NAC over other mucolytics, by suggesting that the effect of NAC on exacerbations is seen only in subjects who are not on ICS.

These recent clinical studies suggest that there may be an interaction of effect on exacerbations between mucolytics and ICS, and that use of ICS may obscure any beneficial effect of the mucolytic. The comparative effects of 10 weeks of fluticasone 1000 µg/day and NAC 600 mg on markers of inflammation and oxidative stress in subjects with COPD have been reported recently (Sadowska et al 2005). NAC decreased IL-8 levels via pathways not involving whole blood glutathione peroxidase or plasma antioxidant activity. Fluticasone did not affect IL-8 levels, but led to a significant increase in antioxidant activity of glutathione peroxidase and plasma antioxidants. These findings suggest, as would be predicted, that the two agents act differently. More research is needed to unravel the complex series of events in the pathogenesis of COPD and exacerbations, and relative effectiveness of agents or combinations of agents. At a clinical level the relative effectiveness of mucolytics vs tiotropium or ICS on exacerbations has not yet been studied. RCTs comparing treatment arms of combination and single agent therapy are warranted.

Mucolytics do not appear to have any convincing effect on lung decline in COPD. The extent to which lung mucus is associated with lung function decline in COPD remains controversial, although a relationship between the two has been shown (Vestbo et al 1996). Because oxidative stress plays a major role in the pathogenesis of COPD (Rahman and MacNee 1996), it was hoped that antioxidants might be beneficial in terms of disease modification through reduction of this stress. The oxidants derive from inhaled cigarette smoke, as well as from tissue macrophages, and neutrophils. If there were a role, it would seem desirable to use mucolytic agents relatively early in the course of the disease while lung function is relatively preserved. The study that had the greatest power to show this (Decramer et al 2005) did not show any

effect of 600 mg NAC daily on FEV_1 decline in a patient population with relatively mild disease. Nor was there any effect of NAC in the more severe COPD subgroup. The authors commented that there was small reduction in FRC seen with NAC which may have occurred through an effect on the small airways. They also propose that the dose of NAC may not have been high enough. There is a recent report of study involving 198 patients with pulmonary fibrosis (Demedts et al 2005) showing a small but significant preservation of lung function in the group treated with NAC 600 mg 3 times daily for 1 year in addition to usual therapy, compared with the group treated with placebo. Clearly the effect of NAC in this disorder is not due to mucolytic properties.

Conclusions

A cost-effectiveness analysis of NAC in CB was performed retrospectively (Grandjean et al 2000a). This was based on direct costs of NAC treatment and management of an acute exacerbation, and indirect costs of sick leave. This suggested that the point at which the costs of treatment and nontreatment were equal was when there was a reduction of 0.6 exacerbations per 6-month period. In the Cochrane review, the overall effect size was a reduction of about 0.4 per 6-month period, suggesting that it would not be cost-effective to treat everyone with COPD with mucolytics.

In their favor, mucolytic agents are safe and very well tolerated with no suggestion from any of the RCTs over 2 months in duration of an increase in adverse effects over placebo. The question of compliance also needs to be considered, as patients would need to take these agents at least daily through the winter months. However, for some patients they may be easier to take than regular inhaled doses of tiotropium or ICS. A further role might be in patients with frequent exacerbations who have adverse effects from these other agents. It is, of course, important to remember that tiotropium improves symptoms whereas mucolytics and ICS will have only a slight effect, if any.

The relative costs of the treatments and medicine availability are other considerations. In New Zealand, tiotropium 18 μg daily is more than double the price of either fluticasone 500 μg/day or the only available mucolytic in tablet form, bromhexine (Adis International 2003).

As there is no evidence of significant disease modification with these agents, treating everyone with COPD with mucolytics is not warranted. The aim of regular treatment with mucolytic agents should be to reduce exacerbations in patients with moderate or severe COPD who have frequent or prolonged exacerbations, or those who are repeatedly admitted to hospital. They might be considered in patients who are unable to take tiotropium or ICS for whatever reason. The evidence is strongest for the use of NAC 600 mg daily for at least 3 months of the year, including the winter months. Whether there are add-on benefits of mucolytic agents to these other medicines is not yet known. Studies to address this, as well as the optimum dose and duration of therapy with agents such as NAC will be helpful in developing a greater range of effective therapies and a better understanding of the pathogenesis of COPD.

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