

## Mucolytics

There are many sufferers from Chronic Obstructive Pulmonary Disease (COPD) in the United Kingdom (UK). COPD accounts for more than 30,000 deaths and over 100,000 hospital admissions per year. Following guidance for the management of COPD from the UK National Institute for Health and Clinical Excellence (NICE) in 2004,<sup>1</sup> and with a new National Service Framework for COPD currently being developed, the focus on the diagnosis and management of this disease has never been higher.

COPD is characterised by airflow obstruction which is usually progressive, not fully reversible, and does not change markedly over several months. The disease is predominantly caused by smoking. COPD is now the preferred term for the conditions in patients with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema. The primary cause of COPD is long-term smoking and many patients suffer from excessive mucus production. Mucus production is part of the pathophysiological picture and is associated with poorer health care outcomes and increased rate of exacerbations. In turn, exacerbations lead to increased morbidity, poorer quality of life and escalating health care costs.

### History and Evolution of Mucolytics

In some European countries mucolytic therapy has been widely used to treat symptoms and frequency of exacerbations of COPD. By contrast, in the UK, mucolytics have previously been used infrequently because they were perceived to be ineffective. However, a Cochrane review in 2001 concluded that treatment with mucolytics produces a small but significant reduction in the number and length of exacerbations.<sup>2</sup> It is not widely appreciated that this review led to

the removal of oral mucolytics from the NHS prescribing blacklist by the Department of Health (DoH) in 2003.

### What are Mucolytics?

Mucolytic agents reduce sputum production and viscosity. Preparations available on prescription in the UK include carbocisteine, mecysteine, and - more recently - erdosteine. Carbocisteine's mode of action is based on the activity of the muco-secreting cells and/or its effect on mucociliary clearance. Mecysteine's mode of action is unknown, while erdosteine, in addition to working as a mucolytic, has anti-adhesive and antioxidant properties.

### What is the evidence for their effectiveness?

An updated and thorough review of the recent evidence on oral mucolytic therapy has been carried out by the Cochrane Collaboration in 2006, which includes randomised trials that compared oral mucolytic therapy with placebo for at least two months in adults with COPD.<sup>2</sup> These trials demonstrated that mucolytic therapy is associated with a reduction in acute exacerbations of COPD, reduced need for antibiotics, fewer days of illness and an improvement in cough, dyspnoea and mucus expectoration. Although these are good quality clinical studies they have their limitations in that most were carried out for periods of six months or less and excluded patients with more severe disease and patients over the age of 66. The authors concluded: *"In subjects with chronic bronchitis or COPD, treatment with mucolytics was associated with a small reduction in acute exacerbations and a reduction in total number of days of disability. Benefit may be greater in individuals who have frequent or prolonged exacerbations, or those who are repeatedly admitted to hospital with exacerbations with COPD. They should be considered for use, through the winter months at least, in patients with moderate or severe COPD*

*in whom inhaled corticosteroids (ICS) are not prescribed."*

Other clinical trials on acute use of oral mucolytics have demonstrated a synergistic effect between erdosteine and concomitant antibiotic therapy when treating infection.<sup>3,4</sup>

### How are they taken?

(Please consult the SPC before prescribing).

Mucolytics are taken as oral tablets. Carbocisteine and mecysteine hydrochloride are licensed for the management of chronic productive cough; a month's trial of treatment is given at an initial fixed dose (1125mg bd and 200mg tds respectively) and subsequently reduced to a maintenance dose. Erdosteine is specifically licensed for the symptomatic treatment of acute exacerbations of chronic bronchitis and is given at a fixed dose of 300mg twice daily for a maximum of 10 days.

All preparations should be swallowed whole. Carbocisteine is also available in syrup form.

### Use of mucolytic therapy in acute exacerbations of COPD

There is some evidence to support the use of mucolytic therapy in acute exacerbations of COPD. All available UK mucolytic preparations may be used to treat symptoms of productive cough during acute exacerbations of COPD. There is evidence from a double-blind, parallel group comparison of erdosteine plus amoxicillin or placebo, that erdosteine has a fast onset of action.<sup>3</sup> It has also been demonstrated that erdosteine inhibits bacterial adhesion to epithelial cells and may increase the speed with which patients recover from acute infective exacerbations of COPD.<sup>3,4</sup>

### Use of mucolytic therapy in the chronic management of COPD

Both carbocisteine and mecysteine

hydrochloride are licensed for the management of chronic productive cough associated with COPD. The NICE guideline<sup>1</sup> recommends that the use of mucolytic therapy in this situation may be indicated after appropriate initial assessment. If symptoms improve following a trial of therapy, and there are no unacceptable side effects, then treatment should be continued at the minimum dose required to achieve symptom control and reviewed after one month and annually thereafter. Treatment with these products starts at a higher dose with a rapid step down to maintenance therapy.

### Side Effects

Side effects of the oral mucolytics are mainly gastrointestinal upset and skin rashes, though side effects are uncommon. The Cochrane review demonstrated that in the included studies, patients prescribed mucolytics were less likely to have an adverse effect than those on placebo (odds ratio 0.79).

### How long should they be taken in the chronic management of COPD?

This is unclear, because most studies to date were of short duration. It would appear from the studies in the Cochrane review that the maximum benefit appears in the first two or three months and then tapers off after that, but does not disappear. Only one study reported in the Cochrane review continued for 24 months. A recent study from Italy demonstrated no exacerbations over the summer period in either the placebo or active group, but it would be unwise to extrapolate these results to the UK with its vastly different climatic and nutritional environment. Similarly, the results of a long-term 36-month trial involving 500 patients in ten different European countries (the BRONCUS trial)<sup>5</sup> failed to show any significant slowing of the decline in FEV<sub>1</sub> over time.

### Who should be receiving oral mucolytic therapy?

The recent NICE COPD guidelines recommend their use in patients with a chronic cough productive of sputum (evidence grade B). It should be noted that recent studies suggest that only about 50% of exacerbations come to the attention of a health care professional but that each exacerbation is accompanied by a decline in lung function and quality of life. One study from Europe also demonstrated a decreased rate of re-hospitalisation for COPD in the group actively treated with a mucolytic agent. There is some evidence<sup>5,6</sup> to suggest that there may be an interaction of effect on exacerbations between mucolytics and concomitant use with inhaled corticosteroids (ICS) and that the use of ICS may obscure any beneficial effect of the mucolytic drugs; however, more research is needed.

### What are the current research needs in the UK?

'Real-life' trials using mucolytics need to be done in a primary care setting:

- In patients who have more severe COPD (FEV<sub>1</sub> <60%)
- For longer duration (acute and chronic use of the drugs)
- To establish whether they should be taken intermittently or continuously.
- To review efficacy with and without concomitant ICS and/or antibiotics

### Summary

Mucolytics are an effective intervention in the management of patients with COPD. They have been used extensively in the rest of Europe, and many studies - summarised in the Cochrane review - have demonstrated their benefits. Their use has been endorsed by National Centre for Clinical Excellence (NICE).

Before prescribing any of these drugs, please refer to the relevant SPC (summary of product characteristics).

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