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The Role of Anticholinergics in 'Stable' Chronic Obstructive Pulmonary Disease: Unanswered Questions

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Chronic obstructive pulmonary disease (COPD) is a common disorder which causes considerable mortality and morbidity [1]. The disease is characterized by relentless progression and many of its sufferers are deemed to have irreversible airflow limitation because they do not show short-term statistically significant responses to glucocorticoid and bronchodilator drugs. Nevertheless, many patients are prescribed such drugs, often long-term, in the hope of obtaining some form of benefit. Currently available drugs cannot be expected to cure COPD and thus treatment should be targeted at either disease modification, symptomatic improvement or both.

The anticholinergic drugs have been available for several years and the theoretical rationale for their use is well established [2]. Cholinergic nerves are the major broncho-constrictor pathway in human airway. Blockade of this pathway offers potential for a degree of improvement in the airflow limitation of COPD, although the great majority of patients have a genuinely irreversible component because of structural changes within the airways. Recent elegant studies of the muscarinic receptors within the lung have increased understanding of the importance of the cholinergic system in COPD, and have raised the possibility of selective receptor blockade [3]. The clinical use of anticholinergic drugs has been reported in a number of studies. Trials in acute exacerbations of COPD are less numerous than studies in stable disease. The results of these acute studies seem to be conflicting: some show benefit whether combined with β -agonists or given alone, whilst others do not [4-6]. In stable disease the consensus of the trials appears to be that most

patients obtain a degree of symptomatic improvement from anticholinergics and that these drugs may be more effective than β -agonists. Furthermore, ipratropium bromide is usually shown to have a more prolonged bronchodilator effect than standard inhaled β -agonists [7, 8]. The changes in average spirometric measurements achieved tend to be numerically small, e.g. peak increases in forced expiratory volume in 1 s (FEV₁) of 0.15-0.36 litres and decreases in FRC of 0.3-0.6 litres [9]. These changes are close to the spontaneous variation of the measurement and maybe difficult to detect reliably in clinical practice; patients may be thus denied the potential benefit of anticholinergic therapy if prescribing decisions are based solely on the results of clinic spirometric tests. Many of the published studies have not sought information about changes in exercise performance and quality of life; changes in these measures may be more important to patients than small improvements in spirometry. Furthermore, recent studies have shown that improvements in walking distance and symptoms obtained following anticholinergics may not be directly related to changes in FEV₁ [10].

A number of studies have shown that acute β -agonist reversibility does not predict anticholinergic response [11-13]. Further, the use of steroid trials performed on a single occasion to classify patients and plan therapy is debatable. Another point to consider is the demonstration of a wide range of individual anticholinergic responsiveness amongst groups of patients with COPD, perhaps reflecting either differences in muscarinic receptor numbers or resting airway smooth muscle tone [14]. This raises the

question of how to assess the response to anticholinergics. Ideally, a comprehensive assessment should include both objective measurements such as assessment of change in airflow, lung volume, exercise physiology and even reactivity and ventilation perfusion, together with more subjective indices such as exacerbation rate, use of rescue medication, symptom score and Quality of Life Questionnaire. This implies that information from both long- and short-term studies should be available.

It may also be important to decide whether specific groups of patients should be given anticholinergics. This group of drugs has been shown to be of second line importance in the treatment of chronic asthma. In COPD, however, the literature suggests that when compared with β -agonists, greater benefit is derived from anticholinergics in older, nonatopic subjects [15] who have smoked and have relatively more severe lung function impairment [13]. What is meant by the term COPD needs to be accurately defined if clinicians are to be selective about the type of patients for whom they prescribe. Inclusion in many studies involves meeting the ATS criteria [16], which define COPD as a disorder characterized by abnormal tests of expiratory flow that do not change markedly over periods of several months' observation. This definition may allow the inclusion of either patients with chronic asthma who have 'lost' reversibility or those with chronic bronchitis and emphysema whose functional impairment is much less severe than that seen in many UK chest clinics.

A further issue to be resolved is whether anticholinergics should be taken either regularly for prolonged periods (irrespective of short-term reversibility) or simply as required for symptomatic relief. Data from longer term studies are needed to address this question, which is particularly important with the development of longer acting anticholinergic drugs such as oxitropium bromide. This question is under consideration in the Lung Health Study [17] which is assessing whether use of ipratropium bromide can slow down the decrease in FEV₁ over the study period of 5 years. However, some of the patients entering this study have relatively mild COPD and there is also a need for study of the longer term use of anticholinergics in patients with severe airflow limitation.

It is also unclear whether anticholinergics should be combined with inhaled steroids for long-term use in the hope of modifying the natural history of COPD by attempting to reduce both cholinergic tone and airway inflammation. This question may be more important in the light of the results of the Euroscop Study [18] which is attempting to assess the use in COPD of inhaled budesonide in a dose of 400 μ g twice daily over 3 years. If this study shows a benefit for longer term use of inhaled steroids in COPD, a direct comparison with long-acting, long-term anticholinergic therapy will be important.

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