Long-acting β_2-agonists in chronic obstructive pulmonary disease

Carol Llewellyn-Jones

Until recently, the use of long-acting β_2-agonists in chronic obstructive pulmonary disease has been understated. There is now evidence that they may offer benefits beyond bronchodilation. This article reviews the management of chronic obstructive pulmonary disease and looks at the place of long-acting β_2-agonists as a first-line treatment option.

Chronic obstructive pulmonary disease (COPD) is one of the most difficult conditions to treat. It presents a challenge to clinicians seeking to preserve respiratory function in patients for as long as possible. It has recently been suggested that long-acting β_2-agonists may offer benefits in COPD beyond bronchodilation (Johnson and Rennard, 2001). This review collates studies underpinning claims for superiority of long-acting β_2-agonists as bronchodilators of choice for first-line therapy.

COPD is a diagnostic label signifying the presence of chronic, slowly progressive and irreversible airflow obstruction; the term encompasses chronic bronchitis, emphysema, small airway disease and intractable asthma. Its hallmark symptoms are cough, hypersecretion of mucus, dyspnoea which often prevents everyday activity such as walking, and chest tightness. COPD has been diagnosed in around 600 000 people in the UK, giving a 1% prevalence overall (Royal College of General Practitioners et al, 1995). However, this is likely to be an underestimate – one source suggests that only 25% of COPD cases in the general population are diagnosed (Siafakas et al, 1995).

COST TO NHS AND SOCIETY

The total cost of COPD to the NHS has been estimated at £500 million per year. Hospital care is costed at £224 million per year, including £174 million covering emergency admissions for exacerbations. Furthermore, COPD accounts for substantially greater numbers of hospital admissions than asthma. In 1994–95, COPD was the cause of 24 million days of sickness absence from work and £331 million paid in benefit. Adding the value of lost work to employers brings the total economic cost to the nation to £1.5 billion (Calverley and Sandhi, 1998; Bellamy and Booker, 2000).

COPD MANAGEMENT

British Thoracic Society guidelines on COPD are currently being updated in association with the National Institute for Clinical Excellence. The Royal College of Physicians of Edinburgh (RCPE) issued a consensus statement on management of COPD in March 2001, and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), in association with the World Health Organization and the National Institutes of Health, published guidelines in May 2001 (Pauwels et al, 2001).

The importance of smoking cessation as the single most effective means of limiting progression of COPD is critical, as is bronchodilator therapy as first-line treatment. The GOLD guidelines also highlight evidence that the long-acting β_2-agonist salmeterol significantly improves health status at doses of 50 μg twice daily and that long-acting bronchodilators offer patients greater convenience (Pauwels et al, 2001). Furthermore, the guidelines state that combining bronchodilator drugs with different mechanisms and duration of action might increase the degree of bronchodilatation with equivalent or lesser side effects.

The use of a long-acting β_2-agonist in combination with an anticholinergic was studied by van Noord et al (2000). Their study concluded that in patients with severe, stable COPD, long-term treatment with long-acting β_2-agonist alone or plus anticholinergic is safe and effective. There was added benefit from the combination therapy in terms of improvement in airway obstruction but not for improvement in symptom control or need for rescue short-acting β_2-agonist.

Dr Carol Llewellyn-Jones is Consultant Respiratory Physician in the Department of Respiratory, West Wales General Hospital, Glangwili, Carmarthen SA31 2AF

Both RCPE and GOLD recognize the importance of assessing health status among COPD patients, acknowledging that the patient's opinion is equally important as forced expiratory volume in 1 second (FEV_1) measurements when assessing response to treatment.

LUNG FUNCTION

β_2-agonists relax airway smooth muscle by stimulating the β_2-adrenergic receptors. This increases the concentration of intracellular cyclic adenosine monophosphate (cAMP) (Lulich et al 1998). The selective long-acting (12-hour) adrenoceptor agonist salmeterol has a long side chain that binds to the exo-site of the receptor. This characteristic enables it to provide longer lasting bronchodilation than either short-acting β_2-agonists or anticholinergic therapies. Long-acting β_2-agonists, such as salmeterol, are thought to achieve improvements in dyspnoea partly by dilating the bronchioles, as far as is possible in COPD, and by altering the distribution of air within the lung. Ramirez-Venegas et al (1997) propose that gas trapping in alveolar spaces and hyperinflation may be reduced, further enhancing respiratory muscle function and relieving chest tightness, although further studies are needed before this can be fully understood.

According to one large multicentre study, adding salmeterol 50 μg twice daily to existing therapy had a positive effect on airflow obstruction and significantly reduced symptoms (Boyd et al, 1997). Results showed a significant improvement in day and night time symptoms compared with placebo and a significant difference in breathlessness scores after walking for 6 minutes, favouring salmeterol at 8 ($P = 0.024$) and 16 weeks ($P = 0.004$). However, a systematic review of trials has shown that the size of improvement in airway function does not appear to reflect the symptomatic improvement that can occur in some patients with salmeterol in COPD (Appleton et al, 2000).

MEASURING QUALITY OF LIFE

Dyspnoea and its restrictions on daily living activities often seriously impair COPD patients' health-related quality of life. Health status can be measured using the St George's Respiratory Questionnaire (SGRQ), a validated instrument in patient populations (Jones et al, 1992). The consequence of dyspnoea is usually severe, with limitations on levels of activity and social participation leading to increasing isolation. Seemungal et al (1998) reported that exacerbations of symptoms also threaten quality of life as measured on the SGRQ since exacerbations are associated with a significant worsening of symptoms.

Decreasing breathlessness, increasing capacity for physical activity and reducing exacerbations to improve or maintain quality of life are major aims of COPD management. Preferred interventions which enable patients to get an undisturbed night's sleep without symptom breakthrough and which offer greater convenience via less frequent dosing can also make a big difference to patients' quality of life (unpublished data, GlaxoSmithKline, 2001).

NEW STRATEGY IN SYMPTOM RELIEF

New research suggests that an alternative strategy in COPD management may be the early introduction of a long-acting β_2-agonist after salbutamol before anticholinergic therapy, or as an addition to anticholinergic therapy. In a 12-week study involving 411 COPD patients, the long-acting β_2-agonist salmeterol showed greater sustained bronchodilation over 12 hours compared with placebo and ipratropium as measured by FEV1. It also increased the time to first exacerbation and improved health-related quality of life scores compared with placebo (Mahler et al, 1999). Since exacerbations are associated with a decline in health status (Seemungal et al, 1998), increasing the time to first exacerbation should improve quality of life and ability to undertake activities of daily living – a principal objective of COPD management.

The randomized double-blind, double dummy, placebo-controlled, parallel group trial randomized patients to either inhaled salmeterol 50 μg twice daily, inhaled ipratropium 40 μg four times daily or placebo (2 puffs four times daily). Salmeterol relieved both day and night time symptoms and was significantly superior to ipratropium in relief of night time dyspnoea ($P = 0.043$) (Mahler et al, 1999). Recent data have also demonstrated that the long-acting β_2-agonist formoterol is also significantly better than ipratropium in improving health status (Dahl et al, 2001).

DISEASE AND REPAIR MECHANISMS: NEW FINDINGS

Cilia help to prevent infection by moving bacteria and mucus away from the lungs. Smoking impairs ciliary function, allowing mucus to build up. This creates a breeding ground for bacteria, leading to further epithelial disturbance and more lung damage. This ultimately results in further deterioration in lung function and quality of life. Laboratory research suggests

that long-acting β_2-agonists produce a sustained increase in ciliary beat frequency (CBF), which may help prevent accumulation of bacteria at sites of damage and thus assist in preventing infection (Devalia et al, 1992). Cultured human bronchial epithelial cells were exposed to a short-acting β_2-agonist, salbutamol, and a long-acting β_2-agonist, salmeterol, and the effects were compared over time. Salmeterol achieved a significantly prolonged increase in CBF from baseline compared with salbutamol; effects were observed within 15 minutes and persisted over the entire 24 hours studied (Devalia et al, 1992). Currently, there are no published accounts of the effect of formoterol on CBF, but as a long-acting β_2-agonist, it is likely to behave similarly to salmeterol (Johnson and Rennard, 2001).

A double-blind, placebo-controlled trial involving 10 healthy subjects looked at effects of a long-acting β_2-agonist on mucociliary transport (Chambers et al, 1999). Subjects were randomized to inhaled salmeterol 50 μg, placebo or no treatment at all. Mucociliary transport was assessed by looking at the mean time for 20% clearance of initial counts using quantitative gamma scintigraphy and inhaled radiolabelled sulphur colloid saline solution. There was a 60.5% increase in mucociliary transport for the long-acting β_2-agonist compared with placebo ($P < 0.02$). In a separate study, formoterol also significantly increased mucociliary clearance by 46% compared with placebo in 10 bronchitic patients after 6 days (Melloni and Germouty, 1992).

Effective mucociliary clearance plays a key role in lung damage limitation in COPD. It helps to prevent infection by respiratory pathogens, which can cause lasting damage to epithelial cells in both healthy subjects and those with airway obstruction. These studies offer interesting results, but further research is needed to fully understand the clinical significance.

RESPIRATORY EPITHELIAL PROTECTION

Bacterial colonization with organisms such as *Haemophilus influenzae* and *Pseudomonas aeruginosa* frequently cause upper and lower respiratory tract infections and are associated with exacerbations of COPD (Dowling et al, 1997, 1998). Given that bacteria have been shown to preferentially adhere to mucus and damaged cells, Dowling et al (1997, 1998) conducted laboratory studies to assess the possible protective effects of a long-acting β_2-agonist on the respiratory epithelium against bacterial-induced damage.

Toxins associated with bacterial colonization can slow CBF, leading to a build up of mucus and creating an environment favourable to bacteria. Maintaining CBF could protect the epithelium against *P. aeruginosa*- and *H. influenzae*-induced damage by preventing bacterial adherence and reducing the concentration of toxins.

Dowling et al (1997, 1998) showed in vitro that, although salmeterol did not affect the numbers of bacteria adhering to the respiratory mucosa, pre-treatment with salmeterol significantly reduced the amount of damage and loss of ciliated cells caused by *P. aeruginosa* and *H. influenzae* compared with the control. This suggests that salmeterol may be effective in reducing damage to the epithelium and may offer some protection against respiratory infections. The mechanism of salmeterol protection and its clinical relevance is not known and warrants further investigation, although the authors hypothesize that toxins lower intracellular cAMP and that salmeterol may help counteract their effects by raising cAMP. Johnson and Rennard (2001) stated that the effect of formoterol on epithelial protection has not been reported, but if used in sufficient concentrations, it is likely to have similar activity.

FUTURE TREATMENTS FOR COPD

At present, there is no pharmacological treatment available to cure or modify the disease process in COPD. However, long-acting β_2-agonists have been shown to provide statistically significant improvements in lung function and decreased symptoms associated with clinically significant improvements in health status. The new in vitro data outlined here are encouraging. These studies suggest that long-acting β_2-agonists may help improve overall health status in COPD by a number of positive effects other than bronchodilation, e.g. on pulmonary epithelium and airway smooth muscle.

These agents have also been shown to reduce the frequency and severity of exacerbations, and their positive effects on mucociliary clearance and cytoprotective factors may begin to explain this observation. However, further in vivo studies are needed to fully understand how these newly identified mechanisms of action may contribute towards enhancing patients' lung function and health status.

The hope for the future is that new drugs will be developed that can further control COPD symptoms and prevent disease progression. Drugs are needed that will act on proteolytic enzymes, cathepsins and matrix metallopro-

teinases which are responsible for the destruction of lung parenchyma, elastin and subsequent fibrosis and squamous metaplasia. These would undoubtedly alter the course of COPD. In the meantime, available agents of proven efficacy should be used in accordance with the evidence base in ways shown to obtain maximum clinical benefit and, equally important, to enhance quality of life for patients. HM

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KEY POINTS

- Smoking is an undisputed cause of chronic obstructive pulmonary disease (COPD). Smoking cessation is the most cost-effective treatment strategy and should be encouraged as a priority.
- Preventing exacerbations helps protect the lungs from further destruction and preserves quality of life. It has major implications for cost savings by reducing need for hospital admission.
- Long-acting β_2-agonists offer an alternative to anticholinergic therapy in COPD and have proven to improve lung function and reduce risk of exacerbations in the short term, with long-term improvements in health-related quality of life.
- There are encouraging new data showing benefits in mucociliary transport with long-acting β_2-agonists, which may help prevent infection and further lung damage.