EDITORIAL

Tiotropium in the management of chronic obstructive pulmonary disease

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Bronchodilators play an important role in the treatment of chronic obstructive pulmonary disease (COPD) and anticholinergics have a long history as an effective and safe treatment. Two papers in this issue extend the information available on tiotropium, through large studies lasting a year. The study by VINCKEN *et al.* [1], on behalf of the Dutch/Belgian tiotropium study group, shows better results with the long-acting anticholinergic tiotropium than with ipratropium in COPD. A number of previous publications have shown that the prolonged bronchodilator action of tiotropium, found in single dose studies, is maintained with continued use [2–4]. This publication extends shorter studies from the same group [2] and shows that the benefits in spirometry, symptoms, health status and exacerbations were maintained over 12 months of the study. A multi-centre study from CASABURI *et al.* [5], comparing tiotropium with placebo, also confirms the continued effect over 12 months. In addition, tiotropium, compared with placebo, improved health status on COPD-specific measures such as the St George's Respiratory Questionnaire, and general measures, such as the Short Form (SF)-36 [5].

Such larger and longer studies are needed for alternative end points, such as exacerbations. The baseline forced expiratory volume in one second of ~40% predicted in these groups of patients, puts them in the moderate or severe COPD range of current guidelines [6–9]. Despite this level of severity, less than half of the participants in either study had an exacerbation during the year and only ~10% needed admission to hospital.

In the study by VINCKEN *et al.* [1], the change in the baseline spirometry 24 h after the last dose of tiotropium was close to 50% of the maximum change achieved, indicating the suitability of once-daily administration of tiotropium. The availability of a long-acting anticholinergic has been promised for some years and the progress of tiotropium from early patient studies to clinical practice seems to have been slow. Tiotropium has the advantage of a prolonged action and relative selectivity since it dissociates more quickly from muscarinic (M_2) receptors than from M_1 or M_3 receptors [10]. In contrast ipratropium

is nonselective, blocking M_1 , M_2 and M_3 receptors. Blockade of the prejunctional M_2 receptors on cholinergic nerve endings may paradoxically increase acetylcholine release since the receptors are inhibitory autoreceptors.

A significant benefit of inhaled anticholinergics is the low incidence of adverse effects. Although dry mouth is seen more frequently with tiotropium than with ipratropium [1, 3, 5] this is usually mild, often transient and has not caused significant patient withdrawal in most published studies.

Alongside the studies of tiotropium have been the trials of long-acting inhaled β -agonists in COPD. Most of these studies have dealt with salmeterol, which has been shown to produce benefits in terms of bronchodilatation [11], symptoms [12], quality of life [13] and time to first exacerbation [14]. In combination with ipratropium, the other long-acting β -agonist, formoterol, has also been shown to be more effective than salbutamol in COPD, as measured by airflow and symptom changes [15].

When COPD is more than mild, symptoms will be persistent and bronchodilator therapy will usually be used on a regular basis [16]. In these situations, effective long-acting agents should simplify the administration and it is likely that once- or twice-daily administration will improve compliance. Published studies now show that they are also more effective than the short-acting agents on a range of end points. The current studies suggest that when it becomes generally available, tiotropium is likely to become standard anticholinergic therapy in COPD providing more convenient administration with significant benefits over ipratropium.

With the short-acting agents, there has been a long running debate about the comparative merits of anticholinergic and β -agonist bronchodilators in COPD. The availability of the long-acting agents could re-open this debate. It would be interesting to see comparative studies including assessments of quality of life and exacerbations, not just spirometry, although this would require longer, more expensive studies. The eventual practical solution may well be the combination of two long-acting bronchodilators in a condition where reversibility is limited and small changes are worth pursuing. Retrospective analysis of the data from studies of short-acting agents has suggested that exacerbations may be less with the combination or ipratropium alone, than with salbutamol alone [17].

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Exacerbations are an area of increasing interest in COPD. They are difficult to study because they are infrequent and difficult to define. However, exacerbations are the cause of considerable inconvenience to patients and expense to the healthcare system. They are associated with a high rate of hospital admission and the alternatives of intensive home support or early discharge teams, to reduce inpatient stays, are also expensive. In the study by VINCKEN *et al.* [1] exacerbations per patient per year were reduced from 0.96–0.73. The figures on patients having ≥ 1 exacerbation suggest that nine patients need to be treated with tiotropium rather than ipratropium for 1 yr to keep one patient free of exacerbations over the year. Looking in the same way at the numbers of patients needing to be treated with respect to hospital admissions, 23 patients treated with tiotropium for 1 yr would prevent one hospital admission. The figures are very similar in the study by CASABURI *et al.* [5], which compares tiotropium with placebo; seven patients treated to keep one patient exacerbation free for 1 yr and 26 to avoid a hospital admission.

A number of treatments have now been shown to reduce exacerbations in COPD: inhaled corticosteroids in the ISOLDE study [18], mucolytics in the recent Cochrane systematic review [19], long-acting β -agonists [13, 20] and tiotropium [1]. Whether these small but significant individual effects can be combined remains to be seen.

The crop of current studies suggest that: if the cost is not prohibitive, bronchodilatation in moderate chronic obstructive pulmonary disease could move to once-daily tiotropium, with or without twice-daily salmeterol or formoterol; a short-acting β -agonist would be available on top for symptom relief; there will be patient and health service benefits in addition to physiological changes in spirometry and the current guidelines [6–9] will need to be adapted to incorporate the emerging evidence; and the effects of combining these agents with inhaled steroids, theophyllines and newer agents, such as phosphodiesterase-4 inhibitors [21], will need further investigation.

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