Occasional reviews

Long acting β₂ agonists and theophylline in stable chronic obstructive pulmonary disease

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The natural history of chronic obstructive pulmonary disease (COPD) is characterised by an accelerated annual decline in forced expiratory volume in one second (FEV₁). One of the most crucial factors in COPD is therefore the means by which this annual decline can be delayed. Bronchodilator therapy is usually prescribed to relieve the symptoms, reverse airway obstruction and, hopefully, to slow the rate of disease progression and decelerate the decline in pulmonary function. However, the Lung Health Study, in its five year observation of almost 6000 patients at risk of developing COPD, reported that the rate of decline of lung function in smokers with mild to moderate COPD could be significantly slowed by smoking cessation but not by bronchodilator therapy.

Nonetheless, bronchodilators are an important form of treatment to reduce symptoms in COPD. As any improvement in airflow might be extremely important in these patients, the recent BTS guidelines for the management of COPD state that bronchodilators are the cornerstone of symptomatic treatment for the reversible component of airway obstruction. Short acting β₂ agonists used as required are recommended to be tried first in view of their more rapid relief of symptoms. If β₂ agonists do not control symptoms adequately or if regular maintenance therapy is desired, an anticholinergic agent can be added or substituted. The addition of oral theophylline should only be considered if inhaled treatments have failed to provide enough benefit.

**Bronchodilating effect of long acting β₂ agonists in COPD**

A long acting version of β₂ agonists has also been developed. At present, long acting β₂ agonist bronchodilators such as formoterol and salmeterol are an interesting new therapeutic option for COPD, but their role in its treatment is still debated. Salmeterol and formoterol appear to be more effective than short acting β₂ agonists, and in patients with stable COPD, salmeterol is more effective than anticholinergic agents.

In recent years several clinical studies have reported that the protracted treatment of COPD with long acting β₂ agonists can lead to an improvement in respiratory function. Formoterol induced an improvement in airflow limitation after one year of treatment. In three month multicentre trial in adults with reversible obstructive airways disease formoterol (formoterol in dry powder form) in a dose of 12 and 24 µg twice daily was significantly more effective than salbutamol dry powder 400 µg four times daily and appeared to be associated with few adverse effects. It was still active after 15 months of treatment. Airways resistance (Raw) decreased from a mean (SD) of 0.52 (0.26) kPa/l.s (range 0.06–2.11) at day 0 to 0.33 (0.14) kPa/l.s (range 0.06–0.88) at one year (–43.5%). FEV₁ increased from 1.90 (0.80) to 2.54 (0.97) l (33.7%). Salmeterol was compared with placebo over four week periods in a double blind, placebo controlled, crossover study involving 63 patients with moderately severe disease. During salmeterol treatment subjects did better in terms of all the measured parameters than during the placebo period. Thus, morning peak expiratory flow rate (PEFR) increased (12 l/min (95% CI 6 to 17)), symptom score diminished, and use of “rescue” medication fell, but improvement in pulmonary function was modest.

In another study salmeterol produced a small but statistically significant improvement in FEV₁, compared with placebo at six hours after both a single dose of 50 µg (0.16 (95% CI 0.09 to 0.22)) and after four weeks of treatment with salmeterol 50 µg (0.11 (95% CI 0.03 to 0.19)) in patients with COPD. Moreover, a large multicentre study which randomised 674 patients to receive either salmeterol 50 µg twice daily, salmeterol 100 µg twice daily, or placebo for a period of 16 weeks showed that FEV₁, measurements improved moderately (+7%) but significantly in each salmeterol group at the end of the study. Formoterol 12 µg twice daily and salmeterol 50 µg twice daily, both formulated as dry powders, had similar efficacy and safety profiles after a six month treatment period in patients with reversible obstructive airways disease.

Since there is only limited evidence as to the efficacy of long acting β₂ agonists in COPD, the BTS guidelines recommend that use of these bronchodilators be restricted to patients with a demonstrable bronchodilator response to short acting β₂ agonists until more data are available. In our opinion this limitation is no longer justifiable. In fact, we have recently shown that patients with COPD who do not manifest early reversibility to salbutamol can still benefit from salmeterol. We must stress that the lack of correlation between early reversibility to a
short acting β₂ agonist and maximum response to a long acting β₂ agonist in several patients might reflect the poor reproducibility of reversibility tests in these patients. Nevertheless, there is now a body of evidence in the literature showing that these bronchodilators are effective and safe in the management of COPD.

Oral versus inhaled bronchodilators

Optimal control of chronic obstructive airway disorders is usually achieved with treatment based on β₂ adrenoceptor agonist administration, inhalation being the most widely used route. An advantage of administering bronchodilators by inhalation is that they do not have to be distributed to the rest of the body and therefore may be given in very much smaller doses. Aerosols are highly effective, have few side effects, and allow for fine adjustment of dosage to control symptoms. Moreover, by delivering drugs directly to the target organ, a much more rapid effect is achieved. Unfortunately, many patients with chronic obstruction of the airways use their inhaler ineffectively. Poor inhalation technique leads to insufficient bronchodilating effect and, consequently, to the prescription of more or additional medication with a higher probability of side effects and higher costs. In these circumstances, oral treatment may be considered a rational alternative. Unfortunately, the effect of oral β₂ agonists on pulmonary function has not been studied to a significant extent in patients with COPD. We have recently reported that both oral bambuterol and inhaled salmeterol resulted in good bronchodilatation in patients with stable COPD. However, bambuterol, but not salmeterol, caused tremor in several subjects and elicited significant and long lasting tachycardia. Because of the high incidence of side effects, oral β₂ agonists are not recommended unless patients are unable to use inhaled therapy.

Bronchodilating effect of theophylline in COPD

Theophylline is the most frequently prescribed oral bronchodilator for the chronic maintenance treatment of chronic obstructive airway disorders. It was regarded as a first line or frequent second line bronchodilator in chronic bronchitis by 40% of 236 general practitioners in Nottinghamshire (UK). The advantages of theophylline are ease of administration and better compliance with sustained release formulations given once or twice daily. Theophylline is an effective bronchodilator in patients with asthma. Its short term administration results in improvement in flow rates and lung volumes that is correlated with serum levels in a classic dose-response relationship. However, debate continues as to its role in COPD. In fact, in patients with COPD it is not possible to determine concentration-effect curves to theophylline because the reproducibility of the magnitude of the response is dependent on the functional index that has been used, although there is evidence of a modest dose-response effect. Chrystyn and colleagues observed that FEV₁, FVC, and PEFR changed only slightly (about 13%) over the range of doses that induced steady state serum theophylline concentrations of 5–10 µg/ml, 10–15 µg/ml, and 15–20 µg/ml, respectively.

Tsuchino and colleagues suggested that high doses of theophylline may be needed to induce a significant increase in FEV₁. However, even when care is taken to ensure a constant serum concentration, the bronchodilator action is limited in patients with stable COPD with changes in FEV₁ ranging from 0 to 20%. Researchers have tried to identify those patients with COPD who would be most likely to derive benefit from theophylline. One study indicated that an acute FEV₁ response of ≥25% to an inhaled β₂ agonist could accurately predict improvement induced by theophylline, though another showed that the acute FEV₁ response is not an effective measure. In yet another study the change in pulmonary function after theophylline administration correlated with, but was usually smaller than, improvements after use of β adrenergic agents. These small changes in lung function are unlikely to alter the prognosis. One of the reasons why theophylline prescriptions are falling worldwide despite the increase in prescriptions of respiratory drugs generally is probably its inadequate bronchodilator action.

Although these findings suggest that theophylline produces minimal changes in pulmonary function in patients with COPD, some investigators have pointed out a correlation between improvement observed with theophylline and length of treatment. In fact, the bronchodilator effect of theophylline is generally achieved after prolonged treatment. The slow onset of action and the difficulties in achieving stable plasma levels mean that most effects occur after 2–6 weeks rather than after a few hours as is the case with inhaled therapy. The study by Murciano and colleagues, which examined a large number of patients with stable, severe “irreversible” COPD, supports this conclusion. Sixty patients with severe COPD (mean FEV₁ 32% predicted) received either theophylline or placebo for two months. The mean serum concentration of theophylline in the active treatment group was 14.8 mg/l. Theophylline administration resulted in a 13% increase in FEV₁, which was statistically significant compared with the placebo group. Higher awake PaO₂, lower awake PaCO₂, higher sleep SaO₂, improved FEV₁ and lower trapped gas volume were seen with a theophylline level of 11.8 µg/ml after three weeks of treatment. Compared with salbutamol, evening administration of once daily theophylline results in better nocturnal oxygen saturation and an improvement in the overnight change in pulmonary function in patients with COPD after a two week treatment period. Attempts to withdraw theophylline, even at lower levels, should be done with caution because of a possible deterioration in pulmonary function.

Unfortunately, theophylline is a difficult drug to use clinically as there is considerable inter- and intra-individual variation in drug handling. It has a narrow therapeutic margin and the dose...
must be carefully titrated with routine blood monitoring to avoid the occurrence of plasma concentration related adverse effects.\textsuperscript{26} Approximately 10–15\% of patients receiving theophylline will experience gastrointestinal upset, insomnia, or other minor side effect.\textsuperscript{40} Both major and minor side effects are less likely if one resists the temptation to increase the blood theophylline level into the high therapeutic range. A British survey showed that theophylline levels were never checked by 76\% of practitioners at the start of treatment or by 48\% during long term treatment.\textsuperscript{40} It is obvious that this aspect of prescribing may compromise both safety and effectiveness, especially as the rate of absorption of theophylline will differ depending on the sustained release formulation administered.\textsuperscript{41}

Due to toxicity, the use of theophylline as monotherapy in COPD should be restricted to the rare cases where patients cannot adequately administer inhalers.

**Comparison of bronchodilating effect of long acting β\textsubscript{2} agonists with theophylline**

Few studies have compared the bronchodilating effect of long acting β\textsubscript{2} agonists and theophylline. This lack of data might be due to the fact that, on one hand, there is still diffluence concerning the use of long acting β\textsubscript{2} agonists in the management of COPD and, on the other, that theophylline is now considered a third line choice.\textsuperscript{2} Consequently, many investigators assume a comparison between these two classes of bronchodilators to be of little point.

We must stress that the analysis of studies in the literature or in press does not permit one to establish whether the enrolled patients were suffering from bronchial asthma or COPD. However, it is well known that there is difficulty in distinguishing with certainty the difference between subjects with COPD who may show a degree of reversibility and those older subjects with asthma whose reversible airflow obstruction has become more fixed.\textsuperscript{42} There may also be mixtures of asthma and COPD co-existing in any one patient. For this reason we thought it useful to report all studies in our knowledge which have compared long acting β\textsubscript{2} agonists and theophylline in patients with reversible obstructive airways disease. We subsequently subdivided these studies into patients with asthma and those with COPD according to the title of each study.

**COMPARISON IN ASTHMATIC PATIENTS**

Most of the clinical trials evaluated the long term clinical control of asthma\textsuperscript{31} or the impact of these drugs on the control of nocturnal asthma.\textsuperscript{43–45} Some also assessed the effects of long acting β\textsubscript{2} agonists and theophylline on pulmonary function, though this was always considered a secondary outcome. Analysis of the respiratory function indicates an improvement with both long acting β\textsubscript{2} agonists and theophylline, with long acting β\textsubscript{2} agonists possessing only a slight advantage.

A recent meta-analysis of nine controlled studies that compared the efficacy and safety of salmeterol and theophylline showed that, during the second week of treatment, patients receiving salmeterol had a 10 l/min greater increase in mean morning PEFR from baseline (95\% CI 5 to 15) than those receiving theophylline.\textsuperscript{46} Similarly, in the second week the increase in mean evening PEFR from baseline observed with salmeterol was significantly greater than that observed with theophylline. Salmeterol also produced a significantly greater increase in mean morning and evening PEFR than theophylline at weeks 3 and 4.

In particular, salmeterol was significantly more effective than theophylline or placebo in improving mean morning PEFR over the entire 12 weeks (p < 0.02) in 484 adult and adolescent patients with moderate asthma.\textsuperscript{43} Mean predose FEV\textsubscript{1}, improved significantly with salmeterol compared with placebo (p < 0.001); there was no difference between theophylline and placebo. In asthmatic patients treated for 28 days, salmeterol induced a significantly higher increase in FEV\textsubscript{1}, than did theophylline + ketotifen, while no significant differences were found in either FVC or PEFR.\textsuperscript{47} Fjellbirkeland and colleagues\textsuperscript{48} demonstrated that, over a two week period, salmeterol in a dose of 50 µg twice daily was more effective and better tolerated than individually titrated oral doses of sustained release theophylline in the management of moderate asthma, although FEV\textsubscript{1} improved to a similar extent during both treatments. However, the increase in PEFR with salmeterol compared with theophylline was highest in a subgroup of patients new to theophylline therapy.

Paggiaro and colleagues\textsuperscript{49} showed that the effects of both salmeterol and theophylline on pulmonary function in patients with moderate to severe asthma were equivalent after a four week period of treatment. At the end of treatment the changes in PEFR were relatively small and not clinically significant. Nutini and colleagues\textsuperscript{50} also found that both treatments led to an improvement in respiratory function over time. Morning and evening PEFR, FEV\textsubscript{1}, and FVC increased without a significant difference between the two drugs at the end of the study.

D’Amato and colleagues\textsuperscript{51} observed that salmeterol at a higher dosage (100 µg twice daily) was significantly more effective than theophylline in increasing morning and evening PEFR in patients with moderate to severe asthma, and diurnal PEFR variations were reduced starting from the first month of treatment in salmeterol treated patients and from the second month onwards in those receiving theophylline. Both treatments induced improvements in FEV\textsubscript{1} and FVC over the three month treatment period. After the first month FEV\textsubscript{1} increased from a mean (SD) of 1.7 (0.6) l to 2.1 (0.8) l in salmeterol treated patients and from 1.6 (0.5) l to 1.9 (0.8) l in those treated with theophylline. At all the visits during the three month treatment period salmeterol was found to produce a higher adjusted mean response than theophylline, although this difference was never statistically significant.
LONG ACTING β2 AGONISTS AND THEOPHYLLINE IN STABLE COPD

Unfortunately, there are few studies in the literature comparing the bronchodilator effects of long acting β2 agonists and theophylline in patients with COPD. In the short term, the bronchodilatory effect of salmeterol and theophylline in COPD was found to be more effective than theophylline, but the difference between the two drugs became less marked with longer term treatment. However, the different incidence of side effects, which is much higher with theophylline, must be stressed. A recent study found that, although salmeterol recipients were not at greater risk for death or hospitalization, patients using theophylline were at a higher risk of cardiovascular death. The maintenance of bronchodilation with salmeterol was shown to be superior to that of theophylline, although the cost of salmeterol was higher than that of theophylline. A three year study has demonstrated that the use of salmeterol as an add-on therapy in patients with moderate to severe COPD significantly improves health status, quality of life, and PEF, and reduces hospital admissions and acute care visits compared with theophylline. The incidence of arrhythmias and hypoxaemia when using salmeterol is likely that the overall cost of theophylline is lower than that of other bronchodilators after adjusting for baseline risk factors are potentially arrhythmogenic in these patients. However, long term use of theophylline may be further displaced as a use-ful agent in the treatment of COPD.

PROBLEMS RELATED TO THE USE OF LONG ACTING β2 AGONISTS AND THEOPHYLLINE

Many patients with COPD have frequent exacerbations requiring hospitalization and increased use of inhaled bronchodilators. However, the long term use of theophylline may be further displaced as a useful agent in the treatment of COPD. In fact, the incidence of arrhythmias and hypoxaemia when using salmeterol is likely that the overall cost of theophylline is lower than that of other bronchodilators after adjusting for baseline risk factors are potentially arrhythmogenic in these patients. However, long term use of theophylline may be further displaced as a useful agent in the treatment of COPD.

PHARMACOEPIDEMIOLOGICAL AND ECONOMIC ASPECTS OF THE USE OF THEOPHYLLINE AND LONG ACTING β2 AGONISTS IN THE MANAGEMENT OF COPD

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IMPACT OF LONG ACTING β2 AGONISTS AND THEOPHYLLINE ON THE HEART

In our opinion, a very important point that should be emphasized is the possible adverse cardiac effects of β2 agonists and theophylline. Although these agents are an attractive option for bronchorelaxation in COPD, long term use of theophylline may be further displaced as a useful agent in the treatment of COPD. In fact, the incidence of arrhythmias and hypoxaemia when using salmeterol is likely that the overall cost of theophylline is lower than that of other bronchodilators after adjusting for baseline risk factors are potentially arrhythmogenic in these patients. However, long term use of theophylline may be further displaced as a useful agent in the treatment of COPD.
formoterol (12 µg) ensures a relatively higher safety margin than formoterol in a dose of 24 µg. However, neither formoterol nor salmeterol elicit significant cardiovascular effects in normal subjects and patients with reversible airway obstruction. Conversely, theophylline causes tachycardia and serious arrhythmias even at serum concentrations considered to be therapeutic. These findings strongly support limiting the use of theophylline to those patients who are incapable of inhaling drugs as suggested by the ATS. Only studies comparing the effects of the two drug classes on the airways after treatment periods lasting several years will be able to clarify their real impact in the treatment of COPD.

**COMBINED USE OF THEOPHYLLINE AND A LONG ACTING β AGONIST IN PATIENTS WITH COPD**

β-agonists are effective bronchodilators and act predominantly on airway smooth muscle. Recent evidence suggests that β2 receptors in airway smooth muscle are coupled directly to maxi-K channels and may thereby bronchodilate without an increase in cyclic AMP. Theophylline has an anti-inflammatory and immunomodulatory activity that is more important than its bronchodilator action. It has been proposed that the observed anti-inflammatory effects of theophylline could be attributed to phosphodiesterase (PDE) inhibition, and recently type III and IV isoenzymes have been characterised in a number of inflammatory cells. PDE type IV inhibitors, which have anti-inflammatory properties, could also provide bronchodilation when used in combination with lower than usual doses of β2 agonists. It is therefore not surprising that a number of clinical studies support the combined use of theophylline and a β agonist in patients with COPD. For example, theophylline (12.9 µg/ml) and salbutamol improved pulmonary function in patients with irreversible COPD, but the combination was better than either alone. Unfortunately it has yet to be established whether the association of a long acting β2 agonist with theophylline induces an increase in the bronchodilator effect caused by either of the two drugs. Only if this effect were documented could the addition of theophylline to a treatment with long acting β2 agonists be justified. In any case, it has recently been shown that regular theophylline treatment neither prevents nor worsens the development of tolerance to the bronchoprotective effect of salmeterol.

**NON-BRONCHODILATOR ACTIVITY OF THEOPHYLLINE AND LONG ACTING β AGONISTS**

The finding that exercise performance after the 12 minute walking test increased significantly at the end of an eight week treatment with 50 µg salmeterol twice daily but not after orally dose-titrated slow release theophylline twice daily and, moreover, that the rating of daily breathlessness assessed by the oxygen cost diagram was lower only after salmeterol treatment, which also reduced weekly inhalations of rescue bronchodilator, supports the notion that it is unlikely that the useful effects of theophylline occur for reasons other than simple bronchodilation. Nevertheless, we must stress that several studies suggest that the effect of long term theophylline and long acting β agonist use in patients with COPD may go beyond bronchodilation to an improvement in various measures of patients’ functional state and well being. In particular, theophylline may improve mucociliary clearance in the airways, respiratory muscle strength, and right ventricular and left ventricular ejection fraction; it may decrease pulmonary artery pressure, stimulate central respiratory activity, and elicit anti-inflammatory action at concentrations which are therapeutically significant. For example, Mahler and colleagues have shown that theophylline significantly reduced dyspnoea in patients with non-reversible obstructive airway disease without altering lung function. Moreover, Ashutosh and colleagues have reported that theophylline increases respiratory drive in clinically employed doses independently of its bronchodilator or metabolic effects. Theophylline is a respiratory stimulant, a feature that may be of benefit to COPD patients who hypoventilate, particularly overnight. In view of the recent developments in the concept of COPD as a chronic inflammatory disease of the airways, the anti-inflammatory activities of theophylline may play a more important role than the mere bronchodilating properties in its treatment. It is therefore possible that theophylline might also attenuate the airflow limitation caused by airway inflammation in COPD.

**Conclusion**

A point of controversy is whether all the benefits of these two classes of bronchodilators in COPD are class effects. Although both theophylline and long acting β agonists elicit bronchodilation, they have significant pharmacodynamic differences. It is possible that some of these specific properties mediate non-bronchodilator benefits. However, interest in these non-bronchodilator effects should be balanced by an awareness of the possible adverse effects of the drugs. Clarification of the differences in response to these agents in COPD is an essential part of tailoring a management plan to each individual patient, considering that physicians must always choose a drug that is highly efficacious, safe, and inexpensive.

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Long acting β, agonists and theophylline in stable COPD


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