Occasional reviews

Long acting β_2 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 (FEV_1). 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,[1] 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[2] state that bronchodilators are the cornerstone of symptomatic treatment for the reversible component of airway obstruction. Short acting β_2 agonists used as required are recommended to be tried first in view of their more rapid relief of symptoms. If β 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.

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Bronchodilating effect of long acting β_2 agonists in COPD

A long acting version of β_2 agonists has also been developed. At present, long acting β agonist bronchodilators such as formoterol and salmeterol are an interesting new therapeutic option for COPD, but their role in its treatment is still debated.[3] Salmeterol and formoterol appear to be more effective than short acting β agonists[4] and, in patients with stable COPD, salmeterol is more effective than anticholinergic agents.[5 6]

In recent years several clinical studies have reported that the protracted treatment of COPD with long acting β_2 agonists can lead to an improvement in respiratory function. Formoterol induced an improvement in airflow limitation after one year of treatment.[7] In a three month multicentre trial in adults with reversible obstructive airways disease eformoterol (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.[8] It was still active after 15 months of treatment.[9] 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%). FEV_1 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.[10] 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 FEV_1 compared with placebo at six hours after both a single dose of 50 μg (0.16 (95% CI 0.09 to 0.22) l) and after four weeks of treatment with salmeterol 50 μg (0.11 (95% CI 0.03 to 0.19) l) in patients with COPD.[11] 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 FEV_1 measurements improved moderately (+7%) but significantly in each salmeterol group at the end of the study.[12]

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.[13]

Since there is only limited evidence as to the efficacy of long acting β_2 agonists in COPD, the BTS guidelines recommend that use of these bronchodilators be restricted to patients with a demonstrable bronchodilator response to short acting β_2 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.[14] We must stress that the lack of correlation between early reversibility to a

short acting β_2 agonist and maximum response to a long acting β_2 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 β_2 adrenoceptor agonist administration, inhalation being the most widely used route.[15] 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.[16] 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.[17] 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 β_2 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 bronchodilation in patients with stable COPD. However, bambuterol, but not salmeterol, caused tremor in several subjects and elicited significant and long lasting tachycardia.[18] Because of the high incidence of side effects, oral β_2 agonists are not recommended unless patients are unable to use inhaled therapy.[19]

Bronchodilating effect of theophylline in COPD

Theophylline is the most frequently prescribed oral bronchodilator for the chronic maintenance treatment of chronic obstructive airway disorders.[20] It was regarded as a first line or frequent second line bronchodilator in chronic bronchitis by 40% of 236 general practitioners in Nottinghamshire (UK).[21] 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.[22] 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.[23] However, debate continues as to its role in COPD.[3 24] 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,[25 26] although there is evidence of a modest dose-response effect. Chrystyn and colleagues[27] observed that FEV_1, 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.

Tsukino and colleagues[28] suggested that high doses of theophylline may be needed to induce a significant increase in FEV_1. 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 FEV_1 ranging from 0 to 20%.[29] 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 FEV_1 response of $\geqslant$25% to an inhaled β agonist could accurately predict improvement induced by theophylline,[30] though another showed that the acute FEV_1 response is not an effective measure.[31] 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.[32] 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.[33]

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.[24] 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.[29] The study by Murciano and colleagues,[34] which examined a large number of patients with stable, severe "irreversible" COPD, supports this conclusion. Sixty patients with severe COPD (mean FEV_1 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 FEV_1 which was statistically significant compared with the placebo group. Higher awake Pa_{O_2}, lower awake Pa_{CO_2}, higher sleep Sa_{O_2}, improved FEV_1, and lower trapped gas volume were seen with a theophylline level of 11.8 μg/ml after three weeks of treatment.[35] 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.[36] Attempts to withdraw theophylline, even at lower levels, should be done with caution because of a possible deterioration in pulmonary function.[37]

Unfortunately, theophylline is a difficult drug to use clinically as there is considerable inter- and intra-individual variation in drug handling.[38] 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.[39] Approximately 10–15% of patients receiving theophylline will experience gastrointestinal upset, insomnia, or other minor side effect.[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.[21] 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.[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_2 agonists with theophylline

Few studies have compared the bronchodilating effect of long acting β_2 agonists and theophylline. This lack of data might be due to the fact that, on one hand, there is still diffidence concerning the use of long acting β_2 agonists in the management of COPD and, on the other, that theophylline is now considered a third line choice.[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.[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_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[43] or the impact of these drugs on the control of nocturnal asthma.[44–46] Some also assessed the effects of long acting β_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_2 agonists and theophylline, with long acting β_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.[47] 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 ($p \leqslant 0.02$) in 484 adult and adolescent patients with moderate asthma.[43] Mean predose FEV_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_1 than did theophylline + ketotifen, while no significant differences were found in either FVC or PEFR.[44] Fjellbirkeland and colleagues[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_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[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[50] also found that both treatments led to an improvement in respiratory function over time. Morning and evening PEFR, FEV_1, and FVC increased without a significant difference between the two drugs at the end of the study.

D'Amato and colleagues[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_1 and FVC over the three month treatment period. After the first month FEV_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.

COMPARISON IN PATIENTS WITH COPD

Comparisons between theophylline and long acting β_2 agonists in patients suffering from COPD are even more scarce.

Di Lorenzo and colleagues[52] compared the effects of salmeterol 50 μg twice daily for three months with oral dose-titrated theophylline twice daily in 178 patients with chronic bronchitis. The morning PEF increased from a baseline value of 324 l/min to 360.7 l/min three months after salmeterol and from a baseline value of 298.8 l/min to 325 l/min three months after theophylline ($p<0.02$). There was a similar trend for evening PEF but differences were not statistically significant.

A short term (two week) comparison between salmeterol 50 μg twice daily or 100 μg twice daily and orally titrated slow release theophylline in 13 patients with moderate COPD showed that salmeterol was always more effective than theophylline although the differences were not significant.[53] However, salmeterol 100 μg twice daily induced a significant improvement in morning PEFR when compared with theophylline.

A one year Italian multicentre study[54] compared the effects of inhaled salmeterol (50 μg twice daily via Diskhaler) with those of oral dose-titrated slow release theophylline in 138 patients with reversible COPD. Salmeterol was found to be more effective than theophylline for the maximum value of morning PEF, but differences in FVC, FEV_1, and maximum value of evening PEF did not reach statistical significance although the effect of salmeterol was slightly superior to that of theophylline. However, it must be stressed that both asthmatic and COPD patients were enrolled in this study.

Problems related to the use of long acting β_2 agonists and theophylline in COPD

Unfortunately, there are few studies in the literature comparing the bronchodilator effects of long acting β_2 agonists and theophylline in patients with COPD. In the short term the adrenergic agent appears to be more active than theophylline, but the difference between the two drugs becomes less marked with long term treatment. However, the different incidence of side effects, which is much higher with theophylline,[40] evokes the need for a continuous appraisal of the cost/benefit relationship.

For the present time we think that the BTS guidelines[2] are correct in suggesting that theophylline is a third line choice of treatment. However, we do not share the cautious approach to long acting β_2 agonists. In fact, there is now evidence that long acting β_2 agonists are an acceptable option as bronchodilators in the treatment of COPD, although they should not be used for acute shortness of breath.[55] In particular, some of the advantages of theophylline can be found in a long acting inhaled β agonist.[56] For this reason, as the acceptance of these agents becomes greater, theophylline may be further displaced as a useful agent in the treatment of COPD.

PHARMACOEPIDEMIOLOGICAL AND PHARMACOECONOMIC CONSIDERATIONS

It is widely held that, since the cost of long acting β_2 agonists is much higher than that of theophylline, the use of methylxanthines is preferable in those socioeconomic systems where, through cost or non-availability, it constitutes the most feasible means of controlling airway obstruction.[57] However, we do not agree with this approach because the price of drugs is only a part of the total cost of treatment and it is likely that the overall cost of theophylline is greater than that of other bronchodilators owing to its toxic effects. In fact, it has been documented that the total cost per year, including admission to hospital for toxic events and monitoring blood levels, was higher for patients using theophylline despite the higher purchase price of other bronchodilators.[58] These considerations could have important clinical implications at a time when high priority is given to the appropriate allocation of health resources.

A recent study found that, although salmeterol was prescribed preferentially to high risk patients, after adjusting for baseline risk salmeterol recipients were not at greater risk than theophylline recipients for severe non-fatal asthma.[59] This finding is important because pharmacoepidemiological studies indicate a strong association between increased β_2 agonist use and β_2 adrenoceptor downregulation and subsensitivity and consequent loss of airway control.[60 61] In particular, Lipworth[62] advised that physicians should be aware of the airway subsensitivity that develops with long acting β_2 agonist therapy and that patients should be warned that they may have to use higher than conventional dosages of short acting β_2 agonists to relieve acute bronchoconstriction in order to overcome this effect. However, we have shown that pretreatment with a conventional dose of formoterol or salmeterol does not preclude the possibility of inducing a further bronchodilation with salbutamol in patients suffering from partially reversible COPD.[63] Bjermet and Larsson[64] have recently reviewed some data related to the debate warning against the use of long acting β_2 agonists and observed that the bronchodilatory effect seems to be fairly stable after regular treatment with these bronchodilators, even though some reports claim that this effect diminishes over time.

IMPACT OF LONG ACTING β AGONISTS AND THEOPHYLLINE ON THE HEART

The impact of bronchodilators on the heart is, in our opinion, a very important point. Cardiac arrhythmias are common in patients with respiratory failure due to COPD. Several factors are potentially arrhythmogenic in these patients including hypoxaemia, hypercapnia, acid-base disturbances,[65] and the use of β agonists or theophylline.[66] We cannot exclude the possibility that adverse cardiac events might occur in COPD patients with pre-existing cardiac arrhythmias and hypoxaemia if they use long acting β_2 agonists, although the recommended single dose of salmeterol (50 μg) and

formoterol (12 μg) ensures a relatively higher safety margin than formoterol in a dose of 24 μg.[67] However, neither formoterol[68] nor salmeterol[69] 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.[70] These findings strongly support limiting the use of theophylline to those patients who are incapable of inhaling drugs as suggested by the ATS.[71] 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_2 agonists are effective bronchodilators and act predominantly on airway smooth muscle. Recent evidence suggests that β_2 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.[72] 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.[73] PDE type IV inhibitors, which have anti-inflammatory properties, could also provide adequate bronchodilation when used in combination with lower than usual doses of β_2 agonists.[74] 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.[75] 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.[76] Unfortunately it has yet to be established whether the association of a long acting β_2 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 β_2 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.[77]

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,[78] supports the notion that it is unlikely that the useful effects of theophylline occur for reasons other than simple bronchodilatation. Nevertheless, we must stress that several studies suggest that the effect of long term theophylline[34] and long acting β agonist[79] 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.[24 80] For example, Mahler and colleagues[81] have shown that theophylline significantly reduced dyspnoea in patients with non-reversible obstructive airway disease without altering lung function. Moreover, Ashutosh and colleagues[82] 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.[83] 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.[84] It is therefore possible that theophylline might also attenuate the airflow limitation caused by airway inflammation in COPD.[85]

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_2 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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