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EVIDENCE-BASED REVIEW

Efficacy of theophylline in people with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis ☆

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Summary *Objectives*: To determine the efficacy of oral theophylline compared with placebo in people with stable chronic obstructive pulmonary disease (COPD).

Methods: Systematic review of randomized-controlled trials comparing oral theophylline with placebo for a minimum of 7 days in people with stable COPD.

Results: Twenty randomized-controlled trials were included in this review. The following outcomes showed significant improvement with theophylline compared with placebo: FEV_1 and FVC both improved with theophylline (weighted mean difference [WMD] 0.10 L; 95% confidence interval [95% CI] 0.04–0.16 and WMD 0.21 L; 95% CI 0.10–0.32, respectively). $\dot{V}O_2$ max also improved with theophylline (WMD 195.27 mL/min; 95% CI 112.71–277.83), as did PaO_2 and $PaCO_2$ (WMD 3.18 mmHg; 95% CI 1.23–5.13 and WMD −2.36 mmHg; 95% CI −3.52 to −1.21, respectively). Patients preferred theophylline over placebo (relative risk 2.27; 95% CI 1.26–4.11). Theophylline increased the risk of nausea compared with placebo (RR 7.67; 95% CI 1.47–39.94).

☆The following Cochrane review has been cited in this evidence-based review: Ram FS, Jones PW, Castro AA, et al. Oral theophylline for chronic obstructive pulmonary disease. The Cochrane Library, Issue 4, 2002. *Copyright Cochrane Library, reproduced with permission.*

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Conclusion: This review has shown that theophylline still has a role in the management of stable COPD, and is preferred by patients over placebo. However, the benefits of theophylline in stable COPD have to be weighed against the risk of adverse effects.

Introduction

Chronic obstructive pulmonary disease (COPD) is, by definition, characterized by limited reversibility with bronchodilator therapy.[1,2] Patients often have major limitations of physical activity, especially breathlessness during exercise. Oral theophylline is a bronchodilator that has been used for many years, although sympathomimetic and inhaled anticholinergic agents are now used more often.[3] Despite this change in prescribing pattern, there is still a perception that theophylline confers additional benefit over that produced by the newer agents.[4]

Theophylline has shown benefit in the management of asthma in both children [5] and adults,[6] but its role in the management of COPD has not been fully defined. Studies have not consistently shown theophylline to be beneficial in the management of stable COPD.[7–9] The British Thoracic Society[10] guidelines on management of COPD recommends use of xanthine derivatives as a last resort, and only after all other treatments have failed to show a response. The American Thoracic Society[1] guideline on COPD makes stronger recommendations for the use of theophylline in both stable and acute management of COPD but, because of its narrow therapeutic index, it also recommends cautious use.[11] Owing to the increasing number of guidelines on the management of COPD, and the lack of evidence-based documentation, the US National Heart Lung and Blood Institute and the World Health Organization have jointly developed evidence-based guidelines for the management of COPD, known as the Global Initiative for Chronic Obstructive Lung Disease or GOLD.[12,13] The GOLD guideline recommends the use of theophylline as a second-line option, because many studies have shown its bronchodilator and non-bronchodilator effectiveness in the management of stable COPD (web address: www.goldcopd.com).

Most trials of oral theophylline in people with COPD have used small numbers of participants. To better evaluate the recommendations from various COPD guidelines and the different conclusions from the many clinical trials, we conducted a systematic review of the literature in order to provide a clearer picture of the efficacy of oral theophylline in people with stable COPD. To our knowledge, no other systematic review of the literature has been published on the use of oral theophylline in stable COPD. This systematic review was originally published electronically in 2002 in the Cochrane Library.[14]

Materials and methods

Types of trials and participants

All included trials were randomized with crossover designs that involved treatment with theophylline or placebo. Trials could include people with any degree of disease severity and lasted 7 days or more. Only trials in people with stable COPD, as defined by internationally accepted criteria,[1,10,15] or defined objectively as a disorder characterized by "reduced expiratory flow and slow forced emptying of the lungs and features which do not change markedly over several months",[15] were considered for inclusion.

Search for trials

A search of the Cochrane database of clinical trials was conducted up until and including April 2004, with no language restrictions. We identified other potential studies by writing to key authors, examining bibliographies of all included studies and relevant review articles. Titles and abstracts of all of the trials identified by electronic searching were assessed independently by two reviewers. The full text copies of all potentially relevant trials were obtained. Any disagreements between reviewers were resolved with discussion.

Methodological trial quality assessment

The methodological quality of all included trials was assessed using two methods: the Cochrane scale for assessment of allocation concealment, and the Jadad[16] quality grading, which evaluates randomization, blinding and dropouts.

Statistical analysis

Individual trial data were pooled using meta-analytical technique where possible. For continuous variables, the results of individual studies were pooled using fixed-effect weighted mean difference (WMD) or standardized mean difference (SMD) with corresponding 95% confidence interval (CI). The WMD is a meta-analytical technique used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group is known. The weight given to each study (e.g. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect. In the statistical software used in this review (RevMan), precision is equal to the inverse of the variance. The WMD technique assumes that all of the trials have measured the outcome on the same scale. The SMD technique is used when an outcome (such as symptom) is measured in a variety of ways across studies (using different scales), and it may not be possible to combine study results in a systematic review. By expressing the effects as a standardized value, the results can be combined, as they have no units. SMD is the difference between two means divided by an estimate of the within-group standard deviation.

Where results were expressed as dichotomous variables, relative risk (RR) with 95% CI was calculated. RR is defined as the ratio of risk in the intervention group to the risk in the control group. An RR of one indicates no difference between comparison groups. For all pooled effects, a test for heterogeneity was carried out using the DerSimonian and Laird method[17], and a $P<0.05$ was considered statistically significant.

Results

Search for trials

From 310 abstracts, 86 full-text papers were retrieved for closer assessment. Twenty-four trials were selected for inclusion. Four trials were multiple publications of the same cohort of patients; therefore, 20 trials were included in the review. Fig. 1 provides details on trial selection.

Characteristics of included participants and concomitant medication

All studies included adults with COPD. COPD was defined using objective criteria of less than 15% in FEV_1 reversibility after inhaling a bronchodilator in six studies[3,9,18–21] or 25% in two studies.[22,23] The Medical Research Council definition of COPD was used in two studies,[18,24] and the American Thoracic Society definition in one.[25] One study[26] did not include patients who had a greater than 20% change in either FEV_1 or FVC over the previous 2 years. Most of the studies also used a pre-defined criteria based on predicted FEV_1 or FEV_1/FVC ratio for including patients in their study; typical values for FEV_1 were less than 60–70% and, for FEV_1/FVC ratio, it was less than 0.6–0.7. One study[25] included patients with a post-bronchodilator FEV_1/FVC ratio of less than 70%. All of the studies included patients who were either ex- or current smokers, and excluded patients who had asthma. Baseline mean FEV_1 for the patients in the 20 studies ranged from 0.96–1.15 L. Mean age ranged from 58–69 years.

Four of the studies did not allow use of bronchodilators during the study period.[7,9,23,26] Twelve studies permitted use of regular bronchodilators and inhaled corticosteroids for the duration of the study period.[3,18,19,24,25,27–33] Four studies did not describe concomitant medication use.[20–22,34]

Efficacy measurements

Thirteen studies with 244 patients contributed data towards FEV_1, which showed significant improvement of 100 L with theophylline (WMD 0.10 L; 95% CI = 0.04−0.16) (Fig. 2). Eleven trials with 196 patients contributed data towards FVC, which showed a significant improvement of 210 L with theophylline (WMD 0.21 L; 95% CI = 0.10−0.32) (Fig. 3). FVC reported as percent predicted by three studies also improved with theophylline (WMD 3.93% predicted; 95% CI = 0.22−7.65). Six studies with 156 patients reported arterial blood gas tensions.[3,7,9,19,27,31] Both PaO_2 and $PaCO_2$ showed significant improvements with theophylline (WMD 3.18 mmHg; 95% CI = 1.23−5.13 and WMD −2.36 mmHg; 95% CI = −3.52 to −1.21, respectively) (Fig. 4 and 5).

Two studies with 32 patients reported VO_2-max,[27,31] which showed significant improvement with theophylline (WMD 195.27 mL/min; 95% CI = 112.71−277.83).

Two trials[3,24] with 100 patients showed greater preference for theophylline compared with placebo (RR 2.27; 95% CI = 1.26−4.11). Three trials reported data on nausea,[3,7,31] with the risk of experiencing nausea significantly increased with theophylline (RR 7.67; 95% CI = 1.47−39.94).

Two studies with 58 patients[18,23] reported distance walked in 6 min (WMD 33.38 m; 95%

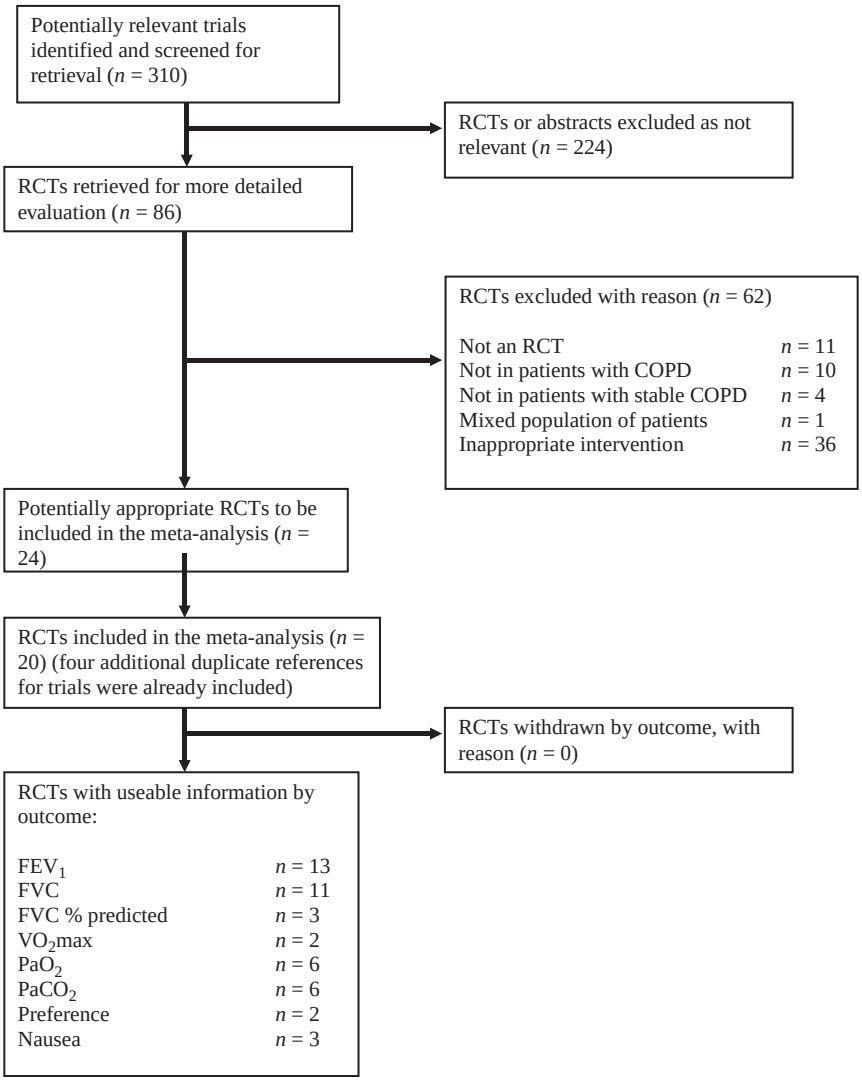

Figure 1 Results of search for trials and reasons for excluding studies.

CI = −11.44 to 78.20), and two studies with 22 patients[19,22] reported distance walked in 12 min (WMD 26.90 m; 95% CI = −8.93 to 62.74). In neither group of studies was the effect significant, and, when all four studies were combined using SMD, the overall effect remained non-significant (SMD 0.30; 95% CI −0.01 to 0.62).

Two studies with 32 patients[18,22] used the 100 mm visual analogue scale to measure breathlessness (WMD 3.61 mm; 95% CI = −4.62 to 11.84). In addition, these two studies[18,22] reported symptoms of wheeze and dyspnoea using ordinal scales (WMD −0.19; 95% CI = −0.58 to 0.19 and WMD −0.32; 95% CI = −0.84 to 0.25, respectively). Other studies also reported symptom as outcomes (e.g. dyspnoea, wheeze and quality of life). However, owing to minimal data reporting and the use of different methodologies, data from these studies could not be collated. Individual studies did, however, report benefits. Alexander et al.[7] used a six-point scale, which measured dyspnoea, wheezing, cough, sputum, walking and feelings that showed improvements in all categories with the use of theophylline. Guyatt et al.[23] reported significant improvements in dyspnoea and quality-of-life scores. In addition, two trials[18,22] reported modest improvement in dyspnoea, another reported significant improvements in dyspnoea scores,[34] and two trials reported improvements in wheezing and shortness of breath with theophylline.[26,30]

Acute exacerbations was reported by two studies with 45 patients,[25,33] showing no significant difference between the theophylline and placebo group (RR 0.33; 95% CI = 0.10−1.14). Unfortunately, no data were reported on health status or mortality.

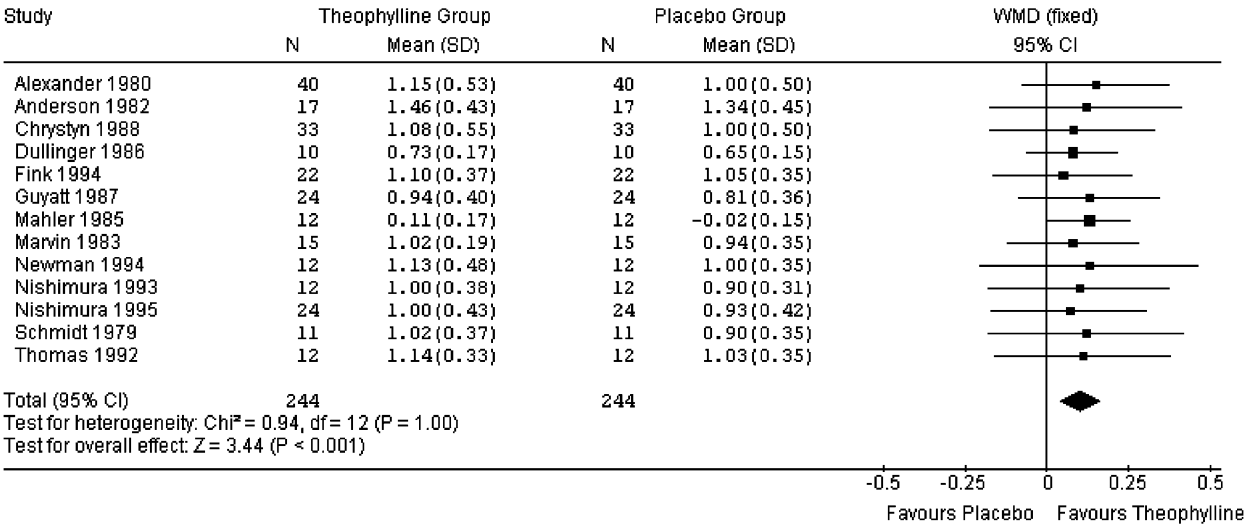

Figure 2 Details of FEV_1 (L). A square box indicates the mean value for each trial with the line through it representing the 95% confidence interval. For this outcome, mean values left of the zero effect line (0) favours placebo and values on the right favours theophylline. The solid diamond indicates the overall mean effect treatment has on FEV_1. The Chi-square value (0.94) and the degrees of freedom value (df = 12) with a *P* value ($P = 1$) at the bottom left of the graph gives a measure of heterogeneity of the combined results that contributed data towards the overall mean result. The z-statistic (3.44) with its *P* value ($P < 0.001$) indicates the level of significance for the overall result.

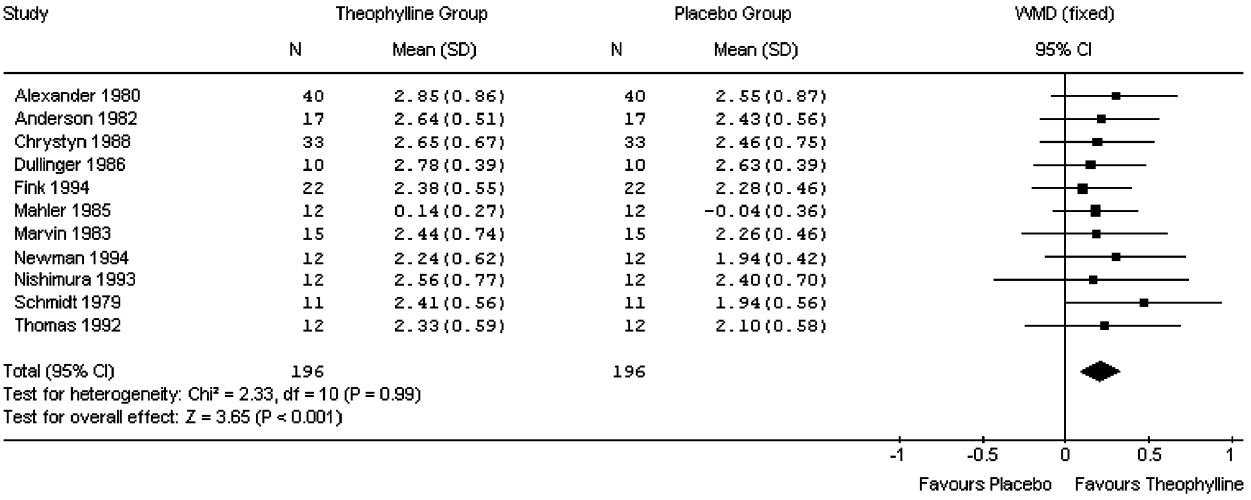

Figure 3 Details of trials contributing data towards FVC (L).

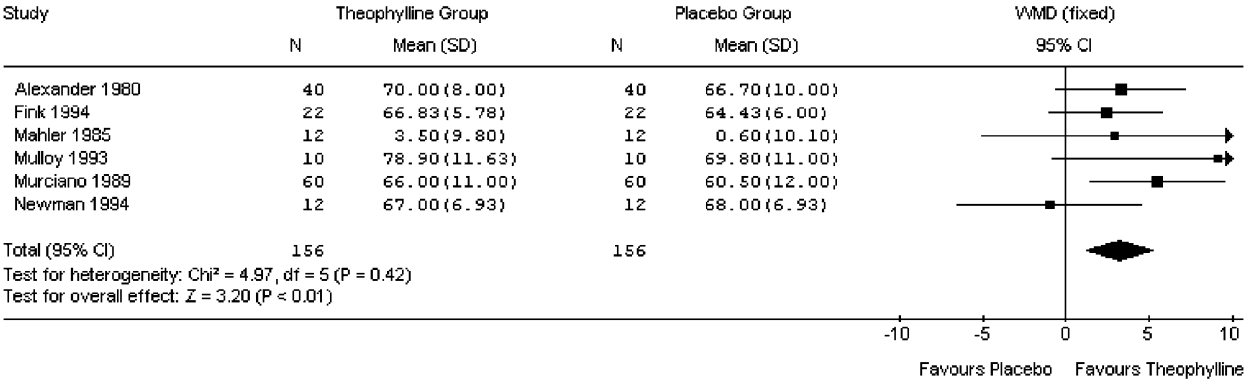

Figure 4 Trials contributing data towards arterial oxygen tension at rest (PaO_2 mmHg).

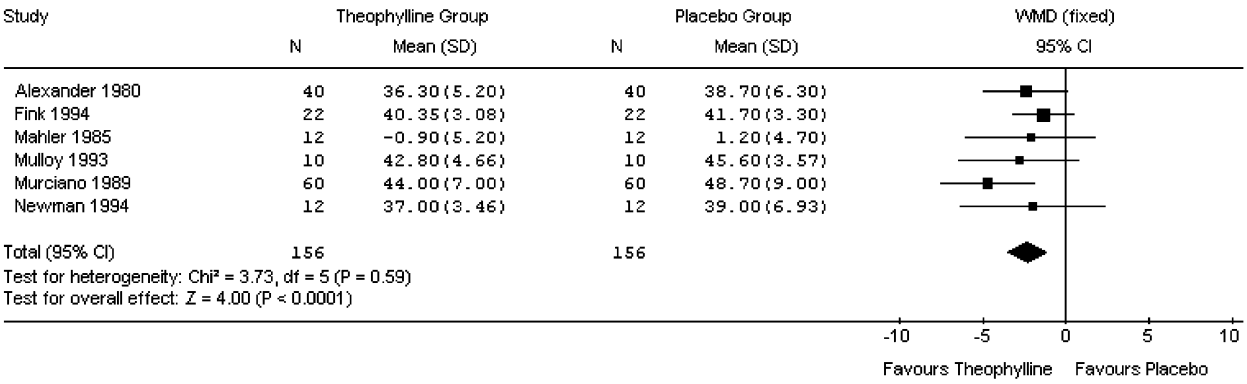

Figure 5 Trials contributing data towards arterial carbon dioxide tension at rest ($PaCO_2$ mmHg).

Discussion

This review has shown that orally administered theophylline for a minimum duration of 7 days to patients with moderate to severe stable COPD improves lung function, ventilatory capacity and arterial blood gas tensions. Although the risk of adverse effects (nausea) was increased with theophylline, patient preference for theophylline was greater than placebo.

The magnitudes of the observed lung function changes are relatively small, and there must be doubt that these alone can explain the large changes reported by individual patients with COPD often treated with theophylline for symptom relief (e.g. breathlessness). Meaningful symptomatic responses from bronchodilators in the presence of trivial changes in FEV_1 and FVC have previously been reported.[19,35,36] Unfortunately, few trials included in this review reported symptoms. The included trials that attempted to measure improvements in symptoms (e.g. dyspnoea, quality of life or wheeze) all showed improvements, but, owing to minimal data reporting and the use of different methodologies, data could not be collated. Individual studies did, however, report benefits.

Other mechanisms have been proposed to explain how theophylline might improve symptoms or reduce breathlessness in patients with COPD. Chrystyn et al.[18] measured the effects of theophylline on 33 patients with stable COPD. In their study, a dose of theophylline that resulted in serum concentrations of 15–20 μg/mL led to a small increase in FEV_1 of 13% (130 mL), but a significant 64% decrease in trapped gas volume (1.84–0.67 L). Unfortunately, this was the only study to report data on trapped gas volume, and further trials are needed.

Other investigators have shown that inhaled β_2-agonists and ipratropium bromide reduce exertional breathlessness in people with stable COPD, and this correlates strongly with decreases in thoracic gas entrapment[18,37] and dynamic hyperinflation.[38,39] The improvements in lung function seen with theophylline in this review may be caused by dilatation of the small airways, with a consequent reduction in gas trapping. A fall in trapped gas volume and thus functional residual capacity is likely to improve the mechanical advantage of the diaphragm and chest wall muscles, and may well explain many of the reported effects of theophylline on the respiratory muscles.[40]

Theophylline has also been shown to increase diaphragmatic strength.[28,41] Its effect has been shown to be greater in a fatigued diaphragm,[40] a phenomenon seen in severe COPD. In one trial, theophylline increased trans-diaphragmatic pressure by 16%, and this increase persisted even after 30 days of treatment with theophylline.[40] In therapeutic doses, theophylline is also known to increase respiratory drive independent of its effect on lung function.[42] Theophylline has also been known to increase respiratory muscle function in normal people[43] and in people with COPD,[41] as measured by increases in maximal inspiratory and expiratory pressures. It has also been suggested that theophylline reduces breathlessness by improving diaphragmatic contractility. Murciano et al.[9] demonstrated an improvement in respiratory muscle performance, as indicated by a decline in the ratio of inspiratory pleural pressure during quiet breathing to the maximal pleural pressure.

Another interpretation is that the improvement in respiratory muscle function is caused by an improvement in the length-tension relationship of the diaphragm because of the reduction in gas trapping, and not because of an increase in diaphragmatic contractility. A recent study by Hatipoglu et al.[44] supports this interpretation. These mechanisms may be responsible for the

slight but significant improvement in lung function seen with theophylline in this review.

Significant improvements were observed in arterial blood gas tensions in patients treated with theophylline. In severe cases of COPD, respiratory rate is increased, and this may be combined with shallow breathing that is pronounced by carbon dioxide retention. It is known that theophylline improves minute ventilation in humans[45] and animals,[46] and also alters the ventilatory response in COPD seen as improved ventilatory capacity measured as increased VO_2 max. This ventilatory response results in an increase in tidal volume, which may be responsible for the improvement seen in blood gas tensions. The increase in VO_2 max and the improved blood gas tensions could be related either to a direct positive inotropic effect of theophylline on the respiratory muscles[28,47–49] or to theophylline's action via a central stimulatory pathway,[50,51] or to both. It is known that theophylline is capable of stimulating the medullary respiratory centre.[52]

Although only two studies provided data for VO_2 max, this is an important significant finding, as greater exercise performance is implied by increases in VO_2 max. Unfortunately, insufficient studies provided data on exercise performance (distance walked, cycle endurance or progressive cycle ergometry) to permit us to relate the increase in VO_2 max to exercise performance.

Theophylline has a narrow therapeutic index, and adverse effects are common even when serum concentrations are in the therapeutic range of 10–20 μg/mL. In this review, significantly more patients treated with theophylline compared with placebo reported nausea. More serious adverse effects of theophylline (e.g. supraventricular arrhythmias[53,54]) were not found in this review. Nevertheless, the benefits of theophylline in stable COPD have to be weighed against the risk of adverse effects. All of the studies included in this review used target theophylline concentrations within the usual therapeutic range. In patients with asthma, theophylline exerts beneficial effects at serum concentrations lower than the traditional therapeutic range of 10–20 μg/mL.[55,56] Lower concentrations of theophylline have the advantage that they are associated with fewer adverse effects. In future trials of theophylline in stable COPD, it may be appropriate to have a lower serum target concentration. An alternative approach would be to study specific inhibitors of type IV phosphodiesterases, which are reported to be effective in the treatment of asthma but which have fewer adverse effects compared with theophylline.[57–59]

Limitations of the review

The small numbers of patients in the included studies, and incomplete reporting of results in the published trials, made it difficult to derive firm conclusions from the review. We wrote to included study authors to obtain further data; however, the response was limited.

There is also a pitfall in including crossover studies, as the presence of carry-over effects of the first treatment into the second treatment period could lead to an underestimation of the real difference among treatments.[60] Nine of the studies reported adequate washout periods between their crossover arms ranging from 3 days to 2 weeks. The remaining 11 studies did not have a washout period or failed to report any washout period. A second possible pitfall associated with crossover designs is that the software we used (RevMan) forces us to analyse crossover studies as if they were parallel studies. It is known[61] that the two methods give identical results if the response to the two treatments in the same individual is completely unrelated, but parallel analysis may lead to decreased statistical power compared with paired analysis if the response to the two treatments is positively correlated (i.e. if patients improving during bronchodilator are also more likely to improve somewhat during placebo). This possibility cannot be discounted in our review. The results of the statistical analysis from two-period crossover trials make two main assumptions: no period effect and no treatment-period interaction. But none of the authors reported these findings (correlation between the responses to the two treatments) from their studies, and the presentation of the data did not permit these types of analysis. Therefore, we cannot exclude that our analysis underestimated the statistical significance of the observed differences, compared with a paired analysis.

Conclusions

This review confirms consistent benefit in improving lung function and arterial blood gas tensions in people with COPD with and without adjuvant bronchodilator therapy. These changes, while modest, were associated with reports from individual studies of improved breathlessness. The mechanism of action of theophylline cannot be determined from this review; however, it supports the actions of theophylline as a ventilatory stimulant and as an agent that reduces trapped gas, as well as a bronchodilator. Despite an increase in adverse

effects, especially nausea, participants preferred theophylline over placebo. With close monitoring of individual patients, it seems that beneficial effects may be obtained in individuals who remain symptomatic from COPD, despite first-line bronchodilator therapy. Theophylline continues to have an important role in the management of symptomatic, stable COPD, in accordance with the approach suggested in recent COPD guidelines.[1,10,13,15]

Larger parallel, randomized-controlled trials with explicit clinical and diagnostic criteria, sufficient duration of follow-up and description of all relevant clinical outcome measures are warranted. Many previously conducted studies have relied heavily on the readily available physiological measurements (e.g., FEV_1, FVC, PEFR). These outcomes are not particularly sensitive measures of change in this group of patients,[36,62] and we suggest that other relevant outcome measures should be used (e.g., trapped gas volume, symptoms, health status, adverse effects, exercise capacity and exacerbations). Future studies should also endeavour to define which ''types'' of patients are most likely to respond to treatment with theophylline. Studies also need to examine the role of theophylline in comparison, and in conjunction, with newer agents such as long-acting bronchodilators. Further investigation of the effect of theophylline on ventilatory mechanics would be helpful to delineate the non-bronchodilator effects of theophylline, which seem to be important. Because of a lower incidence of adverse effects, it will be interesting to observe the efficacy of specific inhibitors of type IV phosphodiesterases in people with COPD.

Practice points

- Oral theophylline remains an important option in the management of stable COPD.
- Theophylline improves lung function, arterial blood gas tensions and ventilatory capacity.
- Patients prefer theophylline to placebo.
- Benefits of theophylline in stable COPD have to be weighed against the risk of adverse effects.

Research directions

- Sensitive measures of change in COPD trials are required.
- There is a need to identify types of COPD patients that are most likely to respond to treatment with theophylline.
- There is a need to examine the role of theophylline in comparison, and in conjunction, with newer agents such as long acting bronchodilators.
- It is important to delineate the non-bronchodilator effects of theophylline.

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References

1. American Thoracic S. American Thoracic Society standards for the diagnosis and care of patients with COPD. *Am J Respir Crit Care Med* 1995;**152**:S77–120.
2. Folgering H, Herwaarden CV. Exercise limitations in patients with pulmonary diseases. *Int J Sports Med* 1994;**15**:107–11.
3. Mulloy E, McNicholas WT. Theophylline improves gas exchange during rest, exercise, and sleep in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1993;**148**:1030–6.
4. Raguso CA, Coggan AR, Labros SS, Gastaldelli A, Wolfe R. Effect of theophylline on substrate metabolism during exercise. *Metabolism* 1996;**45**:1153–60.
5. Yung M, South M. Randomised controlled trial of aminophylline for severe acute asthma. *Arch Dis Child* 1998;**79**:405–10.
6. Wrenn K, Slovis CM, Murphy F, Greenberg RS. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann Intern Med* 1991;**115**:241–7.
7. Alexander MR, Dull WL, Kasik JE. Treatment of chronic obstructive pulmonary disease with orally administered theophylline. A double-blind, controlled study. *J Am Med Assoc* 1980;**244**:2286–90.
8. Eaton ML, Green BA, Church TR, McGowan T, Niewoehner DE. Efficacy of theophylline in ''irreversible'' airflow obstruction. *Ann Intern Med* 1980;**92**:758–61.
9. Murciano D, Auclair M, Pariente R, Aubier M. A randomized, controlled trial of theophylline in patients with severe chronic obstructive pulmonary disease. *N Engl J Med* 1989;**320**:1521–5.
10. British Thoracic Society. British Thoracic Society guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;**52**(Suppl 5):S1–S28.
11. Woodcock AA, Johnson MA, Geddes DM. Theophylline prescribing, serum concentrations, and toxicity. *Lancet* 1983;**1**:610–3.

12. Gomez FP, Rodriguez-Roisin R. Global initiative for chronic obstructive lung disease (GOLD) guidelines for chronic obstructive pulmoary disease. *Curr Opin Pulm Med* 2002;**8**:81–6.
13. Pauwels RA. National and International Guidelines for COPD: The need for evidence. *Chest* 2000;**117**:20S–2S.
14. Ram, FS, Jones, PW, Castro, AA, et al. Oral theophylline for chronic obstructive pulmonary disease. In: The Cochrane Library, Issue 4. Chichester, UK, Wiley; 2002.
15. European Respiratory Society. Optimal assessement and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995;**8**:1398–420.
16. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;**17**:1–12.
17. DerSimonian R, Laird N, DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–8.
18. Chrystyn H, Mulley BA, Peake MD. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ* 1988;**297**:1506–10.
19. Mahler DA, Matthay RA, Snyder PE, Wells CK, Loke J. Sustained-release theophylline reduces dyspnea in nonreversible obstructive airway disease. *Am Rev Respir Dis* 1985;**131**:22–5.
20. Power CK, Morris AM, Sreenan SK, Burke CM. An assessment of oral theophylline in patients with ''reversible'' chronic obstructive pulmonary disease. *Ir J Med Sci* 1992;**161**:509.
21. Schmidt R, Altschuler S. The usefulness of theophylline in nonasthmatic airway obstruction. *Angiology* 1979;**30**:744–9.
22. Dullinger D, Kronenberg R, Niewoehner DE. Efficacy of inhaled metaproterenol and orally administered theophylline in patients with chronic airflow obstruction. *Chest* 1986;**89**:171–3.
23. Guyatt GH, Townsend M, Pugsley SO, et al. Bronchodilators in chronic air-flow limitation. Effects on airway function, exercise capacity, and quality of life. *Am Rev Respir Dis* 1987;**135**:1069–74.
24. Anderson G, Peel ET, Pardoe T, Jones R. Sustained-release theophylline in chronic bronchitis. *Br J Dis Chest* 1982;**76**:261–5.
25. Nishimura K, Koyama H, Ikeda A, Sugiura N, Kawakatsu K, Izumi T. The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. *Chest* 1995;**107**:718–23.
26. Thomas P, Pugsley JA, Stewart JH. Theophylline and salbutamol improve pulmonary function in patients with irreversible chronic obstructive pulmonary disease. *Chest* 1992;**101**:160–5.
27. Fink G, Kaye C, Sulkes J, Gabbay U, Spitzer SA. Effect of theophylline on exercise performance in patients with severe chronic obstructive pulmonary disease. *Thorax* 1994;**49**:332–4.
28. Kongragunta VR, Druz WS, Sharp JT. Dyspnea and diaphragmatic fatigue in patients with chronic obstructive pulmonary disease. Responses to theophylline. *Am Rev Respir Dis* 1988;**137**:662–7.
29. Machraoui A, Lawo T, Schmidt EW, Hoffarth HP, Barmeyer J, Ulmer WT. Ventricular arrythmias in chronic obstructive lung disease (COLD): effect of theophylline in therapeutic doses. *Atemwegs Lungenk* 1994;**20**:510–4.
30. Marvin PM, Baker BJ, Dutt AK, Murphy ML, Bone RC. Physiologic effects of oral bronchodilators during rest and exercise in chronic obstructive pulmonary disease. *Chest* 1983;**84**:684–9.
31. Newman D, Tamir J, Speedy L, Newman JP, Ben-Dov I. Physiological and neuropsychological effects of theophylline in chronic obstructive pulmonary disease. *Isr J Med Sci* 1994;**30**:811–6.
32. Nishimura K, Koyama H, Ikeda A, Izumi T. Is oral theophylline effective in combination with both inhaled anticholinergic agent and inhaled beta 2-agonist in the treatment of stable COPD? *Chest* 1993;**104**:17–184.
33. Rivington RN, Calcutt L, Hodder RV, Stewart JH, Aitken TTL. Safety and efficacy of once-daily Uniphyl tablets compared with twice-daily Theo-Dur tablets in elderly patients with chronic airflow obstruction. *Am J Med* 1988;**85**:48–53.
34. Iversen E, Maltbaek N, Eiken PA, Nielsen LM, Laursen LC, Rasmussen FV. Sustained-release theophylline treatment of patients with irreversible chronic obstructive pulmonary disease. *Eur Respir J* 1992;**5**(Suppl 15):137.
35. Hay JG, Stone P, Carter J, et al. Bronchodilator reversibility, exercise performance and breathlessness in stable chronic obstructive pulmonary disease. *Eur Respir J* 1992;**5**:659–64.
36. Wolkove N, Dajczman E, Colacone A, Kreisman H. The relationship between pulmonary function and dyspnea in obstructive lung disease. *Chest* 1989;**96**:1247–51.
37. Webb K, Fox L, Muir C, O'Donnell DE. Ipratropium bromide reduces exertional dyspnea in patoents with severe chronic airflow limitation. *Chest* 1990;**98**:1135.
38. Belman MJ, Botnick WC, Shin JW. Inhaled bronchodilators reduce dynamic hyperinflation during exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;**153**:967–75.
39. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:542–9.
40. Murciano D, Aubier M, Lecocguic Y, Pariente R. Effects of theophylline on diaphragmatic strength and fatigue in patients with chronic obstructive pulmonary disease. *N Engl J Med* 1984;**311**:349–53.
41. Umut S, Gemicioglu B, Yildirim N, Barlas A, Ozuner Z. Effect of theophylline in chronic obstructive lung disease. *Int J Clin Pharmacol Ther Toxicol* 1992;**30**:149–52.
42. Ashutosh K, Mohammad S, Fragale-Jackson J. Effects of theophylline on respiratory drive in patients with chronic obstructive pulmonary disease. *J Clin Pharmacol* 1997; **37**:1100–7.
43. Sherman MS, Lang DM, Matityahu A, Campbell D. Theophylline improves measurements of respiratory muscle efficiency. *Chest* 1996;**110**:1437–42.
44. Hatipoglu U, Laghi F, Laghi F. Does inhaled albuterol improve diaphragmatic contractility in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999;**160**:1916–21.
45. Darnall-Jr RA. Aminophylline reduces hypoxic ventilatory depression: possible role of adenosine. *Pediatr Res* 1995; **19**:706–10.
46. Javaheri S, Evers JA, Teppema LJ. Increase in ventilation caused by aminophylline in the absence of changes in ventral medullary extracellular fluid pH and carbon dioxide tension. *Thorax* 1989;**44**:121–5.
47. Marsh GD, McFadden RG, Nicholson RL, Leasa DJ, Thompson RT. Theophylline delays skeletal muscle fatigue during progressive exercise. *Am Rev Respir Dis* 1993;**147**: 876–9.
48. Okubo S, Konno K, Ishizaki T, Kubo M, Suganuma T, Takizawa T. Effect of theophylline on respiratory neuromuscular drive. *Eur J Clin Pharmacol* 1987;**33**:85–8.
49. Landsberg KF, Vaughan LM, Heffner JE. The effect of theophylline on respiratory muscle contractility and fatigue. *Pharmacotherapy* 1990;**10**:271–9.

50. Cooper CB, Davidson AC, Cameron IR. Aminophylline, respiratory muscle strength and exercise tolerance in chronic obstructive airway disease. *Bull Eur Physiopathol Respir* 1987;**23**:15–22.
51. Javaheri S, Guerra L. Lung function, hypoxic and hypercapnic ventilatory responses, and respiratory muscle strength in normal subjects taking oral theophylline. *Thorax* 1990;**45**:743–7.
52. Ritchie JM. Central nervous stimulants: the xanthines. In: Goodman Ls GA, editor. *The Pharmacological basis of therapeutics*. New York: Macmillan Publishing Co Inc; 1975. p. 367–8.
53. Levine JH, Michael JR, Guarnieri T. Multifocal atrial tachycardia: a toxic effect of theophylline. *Lancet* 1985;**1**:12–4.
54. Varriale P, Ramaprasad S. Aminophylline induced atrial fibrillation. *Pacing Clin Electrophysiol* 1993;**16**:1953–5.
55. Evans DJ, Taylor DA, Zetterstrom U, Chung KF, O'Connor BJ, Barnes PJ. A comparison of low dose inhaled budesonide plus theophylline and high dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997;**337**:1412–8.
56. Mitenko PA, Ogilvie RI. Rational intravenous doses of theophylline. *N Engl J Med* 1973;**289**:600–3.
57. Compton C, Duggan M, Cedar E, et al. Ariflo® efficacy in a 12 month study of patients with asthma. *Am J Respir Crit Care Med* 2000;**161**:A505.
58. Barnette MS, Underwood DC. New phosphodiesterase inhibitors as therapeutics for the treatment of chronic lung disease. *Curr Opin Pulm Med* 2000;**6**:164–9.
59. Giembycz MA. Phosphodiesterase 4 inhibitors and the treatment of asthma: where are we now and where do we go from here? *Drugs* 2000;**59**:193–212.
60. Cleophas TJ. Carry-over biases in clinical pharmacology. *Eur J Clin Chem Clin Biochem* 1993;**31**:803–9.
61. Cleophas TJ. Crossover trials are only useful when there is a positive correlation between the response to different treatment modalities. *Br J Clin Pharmacol* 1996;**41**: 235–9.
62. Celli BR. The importance of spirometry in COPD and asthma—effect on approach to Management. *Chest* 2000;**117**(Suppl 2):15S–9S.