

A meta-analysis on the efficacy of oral theophylline in patients with stable COPD

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Background: Theophylline is a nonspecific inhibitor of phosphodiesterases that, despite exerting bronchodilator and anti-inflammatory effects, is a third-line therapy rarely used to treat chronic airflow limitation. We wished to evaluate the efficacy of oral theophylline as measured by improvements in trough (pre-dose) or peak (post-dose) FEV₁ and FVC in patients with clinically stable COPD.

Design: Meta-analysis of randomized, placebo-controlled trials reported as of June 2005 in which theophylline was orally administered to stable COPD patients and the functional evaluations included pre- and post-theophylline values for FEV₁ and FVC.

Results: A total of 18 trials were included in the meta-analysis. The weighted mean differences (WMD) with 95% confidence intervals (95% CI) for improvement over placebo in trough FEV₁ and FVC were 0.108L (0.053–0.163) and 0.186L (0.036–0.336), respectively, while peak FEV₁ and FVC improved by 0.096L (0.044–0.147) and 0.242L (0.11–0.374), respectively.

Conclusions: Treatment with oral theophylline improves both trough and peak FEV₁ and FVC in clinically stable COPD patients. These results support previously reported benefits of theophylline in COPD.

Keywords: COPD, meta-analysis, theophylline

Introduction

Theophylline is a nonspecific inhibitor of phosphodiesterases. Since the original report of its efficacy as a bronchodilator, theophylline has been used extensively to treat COPD and asthma (Schultze-Werninghaus and Meier-Sydow 1982). More recently, the importance of its anti-inflammatory properties has been emphasized (Barnes 2003; Barnes et al 2005). Although its use in COPD is recommended in the GOLD Guidelines (Pauwels et al 2001), oral theophylline is rarely prescribed in the Western Hemisphere due to the belief that it is either poorly efficacious, unsafe, or cumbersome in the outpatient setting.

Most of the randomized, controlled trials of theophylline reported in stable COPD patients used a small sample size (Schmidt and Altschuler 1979; Alexander et al 1980; Anderson et al 1982; Marvin et al 1983; Mahler et al 1985; Dullinger et al 1986; Guyatt et al 1987; Chrystyn et al 1988; Berry et al 1991; Thomas et al 1992, 1995; Nishimura et al 1993; Fink et al 1994; Newman et al 1994; Shivaram et al 1997; Tsukino et al 1998; Rossi et al 2002; Broseghini et al 2005) and there is only one systematic review/meta-analysis of the published data (Ram et al 2005). Thus, controversy still exists about its potential risks and benefits. In addition, it is unclear whether any putative benefits of oral theophylline in COPD would be immediate (ie, improvement in peak pulmonary function after dosing), long-term (ie, improvement in trough pulmonary function over time), or both.

We wished to analyze the efficacy of oral theophylline in stable COPD patients. We conducted meta-analyses of the trough and peak FEV₁ and FVC data reported and published as of June 2005 from randomized, placebo-controlled trials in which

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oral theophylline was administered to clinically stable COPD patients. To our knowledge, this approach of analyzing the effects of theophylline on peak and trough pulmonary function has not been reported previously.

Materials and methods

Types of trials and patients

All the trials included involved treatment with oral theophylline in a stable COPD population. Only those published trials involving patients with stable COPD who had pulmonary function tests (PFTs) performed before and after administration of theophylline were included. The articles were evaluated for comparisons of theophylline vs placebo. Specifically, trough and peak FEV₁ and FVC results were of interest.

Search for trials

A search of the PubMed database was performed using the terms “theophylline + COPD” for English language articles published up to and including June 2005. The literature search was limited to randomized controlled trials in humans. The search yielded 66 articles. A review of these articles was conducted for trials involving patients with stable COPD who had PFTs measured as part of the trial. This yielded 17 articles. Of these, 3 did not provide either FEV₁ or FVC data and were excluded from the analysis, and 4 additional papers were active-controlled only (ie, were not placebo controlled) and were also excluded. Additionally, we reviewed a recently published meta-analysis (Ram et al 2005). Since the selection criteria for inclusion of publications in this meta-analysis were similar to our criteria (albeit not identical), additional articles cited by Ram and colleagues that were not identified in our PubMed review were also included. This yielded 8 additional articles. Therefore, a total of 18 trials met the criteria for inclusion in our meta-analysis.

Extraction of data used for meta-analysis

Articles were individually reviewed for the following PFT results: trough FEV₁, trough FVC (pre-dose values), peak FEV₁, and peak FVC (highest values post-dose). Not all articles reported all four of these PFTs and in many cases they did not differentiate between trough and peak. If any of the four PFT results were reported, the article was accepted. In the cases where the authors did not differentiate

between trough and peak, we determined this from the time the last dose of theophylline was taken and the time the PFT was done. The data were extracted from text, tables, and/or graphs.

The mean FEV₁ (trough and/or peak) and FVC (trough and/or peak) in the theophylline group and the placebo group were recorded along with the standard deviation. Additionally, the number of patients participating in each group (n) was recorded (Table 1).

Statistical analysis

Individual trial data were pooled using meta-analytical techniques. Meta-analyses involving continuous outcomes were based on comparisons of means for theophylline vs placebo. For continuous variables (such as trough FEV₁, trough FVC, peak FEV₁, and peak FVC), the results of individual studies were pooled using fixed-effect weighted mean difference (WMD) with the corresponding 95% confidence interval (CI). The WMD is a meta-analytical technique used to combine measures on continuous scales, where the mean, standard deviation and sample size for each group are known. The weight given to each study is determined by the precision (the inverse of the variance) of its estimate of effect. The WMD technique assumes that all of the trials measured the outcomes using the same scales. All statistical analyses were carried out using Comprehensive Meta-Analysis™ Version 2.

Results

Ten studies with 704 patients combined contributed data for the analysis of trough FEV₁ (Figure 1), which showed a significant improvement for theophylline of 108 mL over placebo (WMD 0.108 L; 95% CI=0.05–0.16). Six studies with 166 patients combined contributed data for the analysis of trough FVC (Figure 2), which showed a significant improvement of 186 mL over placebo (WMD 0.186 L; 95% CI=0.04–0.34). Twelve studies with 800 patients combined contributed data for the analysis of peak FEV₁ (Figure 3), which showed a significant improvement of 96 mL over placebo (WMD 0.096 L; 95% CI=0.04–0.15). Ten studies with 358 patients combined contributed data for the analysis of peak FVC (Figure 4), which showed a significant improvement of 242 mL over placebo (WMD 0.242 L; 95% CI=0.11–0.37). For trough and peak FEV₁, the largest contribution of data (400 patients) was derived from a single study (Rossi et al 2002) that showed a significant improvement over placebo of 90 mL and 80 mL, respectively.

Table 1 Characteristics of randomized controlled trials included in the meta-analysis

Author and year	n	Mean age or range ^a	Males/females	Theo dose (mg)	Treatment duration	Baseline FEV ₁ ^b
Schmidt and Altschuler 1979	12	30–70	NR ^c	800/day	3-month crossover	1.0 L
Alexander et al 1980	40	59	40/0	400/day	4-week crossover	<60% predicted
Anderson et al 1982	21	58	17/4	350–700/day	8-day crossover	48% predicted ^d
Marvin et al 1983	15	50–69	15/0	800/day	10 days	1.0 L
Mahler et al 1985	12	60	12/0	Titrated to 10–20 mg/L	4-week crossover	1.36 L
Dullinger et al 1986	10	61	NR	Titrated to 10–15 mg/L	1-week crossover	< 1.0 L
Guyatt et al 1987	19	65	19/0	Titrated to 65–100 mmol/L	14 days	1.0 L
Chrystyn et al 1988	33	53–73	30/3	Titrated to 5–20 mg/L	60 days	< 30% predicted
Berry et al 1991	12	63	12/0	750–1000 mg/day	2 days	1.4 L
Thomas et al 1992	12	63	6/6	Titrated to 10–16.5 mg/L	2-week crossover	1.1 L
Nishimura et al 1993	12	64	11/1	400–600/day	4-week crossover	0.9 L
Newman et al 1994	12	62	11/1	Titrated to 10–20 µg/ml	4 weeks	1.1 L
Fink et al 1994	22	68	17/5	Titrated to >55 µmol/L	4-week crossover	1.0 L
Nishimura et al 1995	24	65	24/0	Titrated to >10 µg/mL	4-week crossover	0.96 L
Shivaram et al 1997	17	66	NR	400/day	Single dose	0.77 L
Tsukino et al 1998	21	65	21/0	600–800/day	3-day crossover	1.0 L
Rossi et al 2002	854	63	709/145	Titrated to 8–20 mg/L	12 months	1.37 L
Broseghini et al 2005	13	67	10/3	Titrated to 10–20 µg/mL	2-week crossover	1.3 L

^amean of whole study population^bmean percent predicted in the study population^cnot reported^dpeak expiratory flow rates

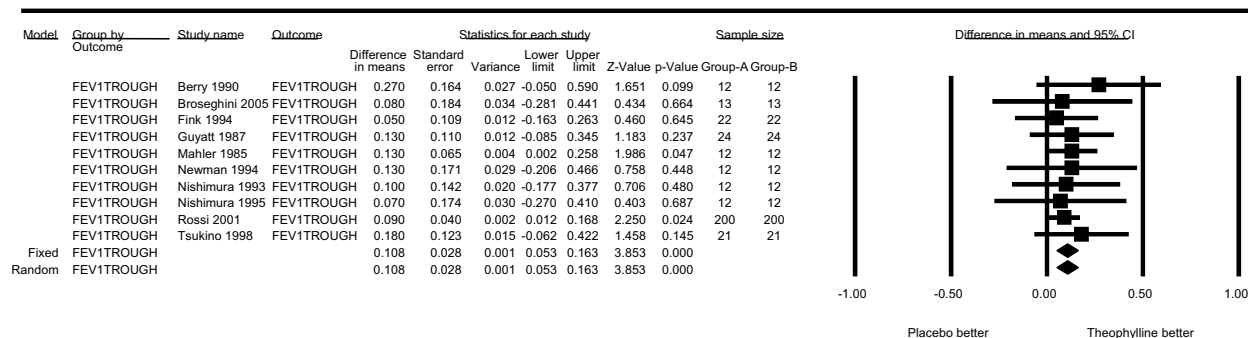
Discussion

Our results show that oral theophylline confers a bronchodilator effect as measured by improvements of trough and peak FEV₁ and FVC in clinically stable COPD patients. One limitation of our study that limits the interpretation of these results is that we did not analyze the incidence of adverse events reported by the patients who received theophylline. However, in a recent meta-analysis that reported similar improvements in pulmonary function to those we are reporting, preference for theophylline was higher than for placebo despite a higher incidence of adverse events (Ram et al 2005).

Our study dissects the improvements in trough and peak pulmonary function tests and shows that the benefits of theophylline are immediate (improvements in peak values) and also sustained (improvements in trough values).

There is debate around the meaning of improvements in trough vs peak pulmonary function, but the debate is more intense concerning the magnitude of such improvements that are clinically meaningful in COPD (Donohue 2004). It is generally agreed that for a particular improvement to be considered of value it needs to be accompanied by clinical improvement. The improvement of 108 mL seen in trough (pre-dose) FEV₁ and of 186 mL seen in trough FVC, as well as the improvements of 96 mL and 242 mL in peak (post-dose) FEV₁ and FVC, respectively, seem comparable to those achieved with other bronchodilators commonly used in COPD. For example, data presented at different US Food and Drug Administration (FDA) Advisory Committee meetings showed that salmeterol provoked an improvement of 90 mL in trough FEV₁ and 200 mL in peak FEV₁. Salmeterol 50 mg/fluticasone 250 mg combination therapy achieved 164 mL in trough FEV₁ and 281 mL in peak FEV₁.

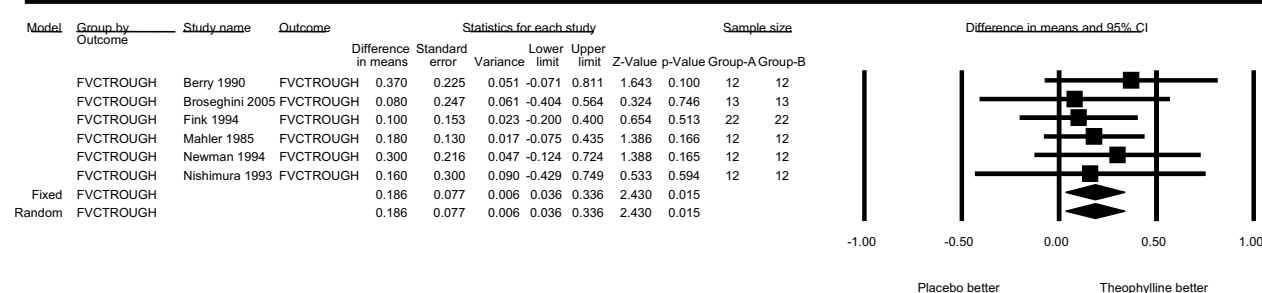
Meta-analysis (WMD): theophylline vs placebo



Comprehensive Meta-Analysis Version 2

Figure 1 Meta-analysis on trough FEV₁ showing results favoring theophylline.

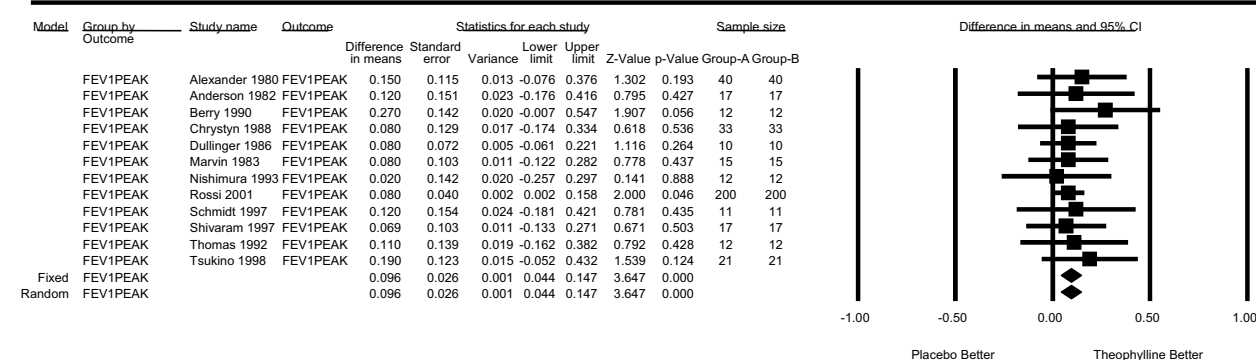
Meta-analysis (WMD): theophylline vs placebo



Comprehensive Meta-Analysis Version 2

Figure 2 Meta-analysis on trough FVC showing results favoring theophylline.

Meta-analysis (WMD): theophylline vs placebo



Comprehensive Meta-Analysis Version 2

Figure 3 Meta-analysis on peak FEV₁ showing results favoring theophylline.

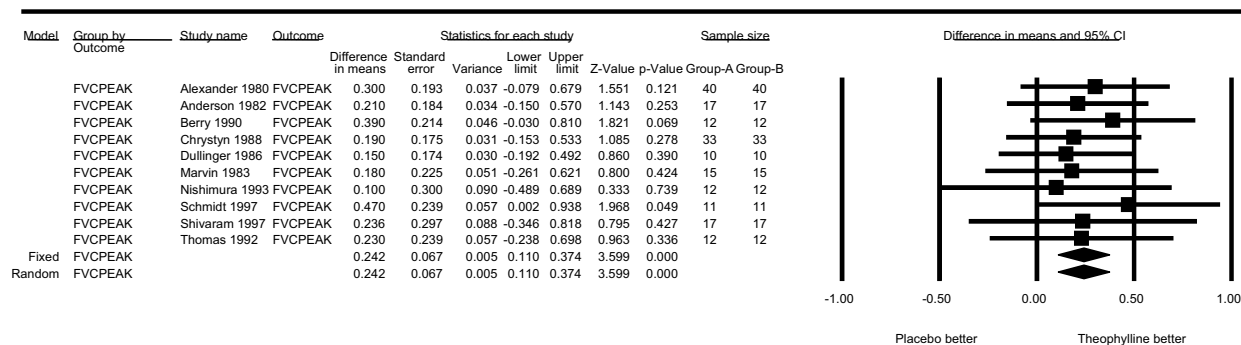
(<http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3830T1.htm>). Tiotropium improved trough FEV₁ by 110–130 mL (depending on the study) and peak FEV₁ by 240–260 mL (<http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3890t1.htm>).

An additive benefit of comparable magnitude can be seen when oral theophylline is used with another bronchodilator

(Table 2). This additive effect may be different from the putative synergistic mechanism proposed by Barnes et al (2003) for the effects of inhaled steroids in COPD (Lim et al 2000; Oliver et al 2001).

In conclusion, it appears that in patients with clinically stable COPD, oral theophylline can improve FEV₁ and FVC. Since blood levels need to be closely monitored and adjusted

Meta-analysis (WMD): theophylline vs placebo



Comprehensive Meta-Analysis Version 2

Figure 4 Meta-analysis on peak FVC showing results favoring theophylline.

Table 2 Studies that have demonstrated a benefit when theophylline is used with another bronchodilator in stable COPD patients

Author (bronchodilator, bd)	Mean % increase FEV ₁ post-bd	Mean % increase FVC post-bd	Mean % increase FEV ₁ post-bd+theophylline	Mean % increase FVC post-bd+theophylline
Thomas et al 1992 (albuterol)	16.2	16.3	31.3	24.9
Tsukino et al 1998 (ipratropium)	17.4	NR	33.3	NR
ZuWallack 2001 (salmeterol)	8	13	17	26.6
Bellia 2002 (oxitropium)	5	4	16	13
Dullinger et al 1986 (metaproterenol)	18.5	11	18.5	14.4

to avert serious, even potentially life-threatening side-effects, theophylline remains a third choice in the COPD therapeutic armamentarium. It remains to be shown whether safer sub-therapeutic doses of oral theophylline can exert any clinically meaningful benefit in COPD, as recently proposed (Barnes 2005).

References

- Alexander MR, Dull WL, Kasik JE. 1980. Treatment of chronic obstructive pulmonary disease with orally administered theophylline. A double-blind, controlled study. *JAMA*, 244:2286–90.
- Anderson G, Peel ET, Pardoe T, et al. 1982. Sustained-release theophylline in chronic bronchitis. *Br J Dis Chest*, 76:261–5.
- Barnes PJ, Adcock IM, Ito K. 2005. Histone acetylation and deacetylation: importance in inflammatory lung diseases. *Eur Respir J*, 25:552–63.
- Barnes PJ. 2003. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med*, 167:813–18.
- Bellia V, Foresi A, Bianco S, et al. 2002. Efficacy and safety of oxitropium bromide, theophylline and their combination in COPD patients: a double-blind, randomized, multicentre study (BREATH Trial). *Respir Med*, 96:881–9.
- Berry RB, Desa MM, Branum JP, et al. 1991. Effect of theophylline on sleep and sleep-disordered breathing in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*, 143:245–50.
- Broseth C, Testi R, Polese G, et al. 2005. A comparison between inhaled salmeterol and theophylline in the short-term treatment of stable chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*, 18:103–8.
- Chrystyn H, Mulley BA, Peake MD. 1988. Dose response relation to oral theophylline in severe chronic obstructive airways disease. *BMJ*, 297(6662):1506–10.
- Donohue JF. 2004. Therapeutic responses in asthma and COPD. *Bronchodilators. Chest*, 126(Suppl):S125–37.
- Dullinger D, Kronenberg R, Niewoehner DE. 1986. Efficacy of inhaled metaproterenol and orally-administered theophylline in patients with chronic airflow obstruction. *Chest*, 89:171–3.
- Fink G, Kaye C, Sulkes J, et al. 1994. Effect of theophylline on exercise performance in patients with severe chronic obstructive pulmonary disease. *Thorax*, 49:332–4.
- Guyatt GH, Townsend M, Pugsley SO, et al. 1987. Bronchodilators in chronic air-flow limitation. Effects on airway function, exercise capacity, and quality of life. *Am Rev Respir Dis*, 135:1069–74.
- Lim S, Jatakanon A, Gordon D, et al. 2000. Comparison of high dose inhaled steroids, low dose inhaled steroids plus low dose theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax*, 55:837–41.
- Mahler DA, Matthay RA, Snyder PE, et al. 1985. Sustained-release theophylline reduces dyspnea in nonreversible obstructive airway disease. *Am Rev Respir Dis*, 131:22–5.
- Marvin PM, Baker BJ, Dutt AK, et al. 1983. Physiologic effects of oral bronchodilators during rest and exercise in chronic obstructive pulmonary disease. *Chest*, 84:684–9.
- Newman D, Tamir J, Speedy L, et al. 1994. Physiological and neuropsychological effects of theophylline in chronic obstructive pulmonary disease. *Isr J Med Sci*, 30:811–16.
- Nishimura K, Koyama H, Ikeda A, et al. 1993. Is oral theophylline effective in combination with both inhaled anticholinergic agent and inhaled beta 2-agonist in the treatment of stable COPD? *Chest*, 104:179–84.
- Nishimura K, Koyama H, Ikeda A, et al. 1995. The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. *Chest*, 107:718–23.

- Oliver B, Tomita K, Keller A, et al. 2001. Low-dose theophylline does not exert its anti-inflammatory effects in mild asthma through upregulation of interleukin-10 in alveolar macrophages. *Allergy*, 56:1087–90.
- Pauwels RA, Buist AS, Ma P, et al. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care*, 46:798–825.
- Ram FS, Jardin JR, Atallah A, et al. 2005. Efficacy of theophylline in people with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Respir Med*, 99:135–44.
- Rossi A, Kristufek P, Levine BE, et al. 2002. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest*, 121:1058–69.
- Schmidt R, Altschuler S. 1979. The usefulness of theophylline in nonasthmatic airway obstruction. *Angiology*, 30:744–9.
- Schultze-Werninghaus G, Meier-Sydow, J. 1982. The clinical and pharmacological history of theophylline: first report on the bronchospasmolytic action in man by S. R. Hirsch in Frankfurt (Main) 1922. *Clin Allergy*, 12:211–15.
- Shivaram U, Cash ME, Mateo F, et al. 1997. Effects of high-dose ipratropium bromide and oral aminophylline on spirometry and exercise tolerance in COPD. *Respir Med*, 91:327–34.
- Thomas P, Pugsley JA, Stewart JH. 1992. Theophylline and salbutamol improve pulmonary function in patients with irreversible chronic obstructive pulmonary disease. *Chest*, 101:160–5.
- Tsukino M, Nishimura K, Ikeda A, et al. 1998. Effects of theophylline and ipratropium bromide on exercise performance in patients with stable chronic obstructive pulmonary disease. *Thorax*, 53:269–73.
- ZuWallack RL, Mahler DA, Reilly D, et al. 2001. Salmeterol plus theophylline combination therapy in the treatment of COPD. *Chest*, 119:1661–70.