

Review: Methylxanthines are not effective for acute exacerbations of chronic obstructive pulmonary disease

Barr RG, Rowe BH, Camargo CA Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomised trials. *BMJ*. 2003;327:643-8.

QUESTION

In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), what is the effectiveness of the addition of methylxanthines to standard treatments?

DATA SOURCES

Studies were identified by searching the Cochrane Airways Review Group COPD trials register {March 2003}* (assembled from searches of MEDLINE, EMBASE/Excerpta Medica, and CINAHL), scanning bibliographies of relevant studies, and contacting authors.

STUDY SELECTION AND ASSESSMENT

Studies were selected if they were randomized controlled trials (RCTs) that compared methylxanthines (oral theophylline, intravenous aminophylline, or intravenous doxofylline) with placebo for acute exacerbations of COPD; treatment occurred in the emergency department (ED) or immediately after admission to hospital; and patients had confirmed COPD with an exacerbation that required presentation to an ED, acute care setting, or hospital. Studies were assessed for methodologic quality using the Cochrane approach and Jadad criteria.

OUTCOMES

Change in FEV₁ at 2 hours and at 3 days, clinical endpoints (e.g., admission to hospital, relapse within 7 d, and length of hospital stay), change in self-reported symptom scores, and adverse events.

MAIN RESULTS

4 RCTs (169 patients) reported between 1984 and 2000 met the selection criteria. 2 RCTs recruited patients presenting to EDs, and 2 recruited patients admitted to hospital. 3 RCTs evaluated intravenous aminophylline, and 1 evaluated oral theophylline. Change in FEV₁ was similar in the methylxanthine and placebo groups at 2 hours but was greater in the methylxanthine group at 3 days (weighted mean difference 101 mL, 95% CI 26 to 177 mL) (2 RCTs). Methylxanthines and placebo did not differ for changes in symptom scores over 3 days.

Also, methylxanthines and placebo did not differ for rates of relapse within 7 days (2 RCTs), palpitations or arrhythmias (2 RCTs), or tremor (3 RCTs), but methylxanthines were associated with more nausea or vomiting than placebo (3 RCTs) (Table).

CONCLUSION

In patients with acute exacerbations of chronic obstructive pulmonary disease, methylxanthines do not improve lung function after 2 hours, clinical outcomes, or symptoms and increase nausea or vomiting.

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*Information provided by author.

Methylxanthines vs placebo for acute exacerbations of chronic obstructive pulmonary disease†

Outcomes	Weighted event rates		RRI (95% CI)	NNH (CI)
	Methylxanthines	Placebo		
Relapse within 7 days	13%	11%	43% (-47 to 287)	Not significant
Nausea or vomiting	37%	14%	163% (35 to 415)	6 (4 to 14)
Palpitations or arrhythmias	18%	5%	262% (-15 to 1446)	Not significant
Tremor	42%	33%	31% (-13 to 97)	Not significant

†Abbreviations defined in Glossary; weighted event rates provided by author. RRI, NNH, and CI calculated from data in article using a fixed-effects model. Follow-up period for outcomes varied by trial.

COMMENTARY

It was not so long ago that most experts recommended theophylline as a first-line agent for treating both stable and exacerbated COPD. Theophylline use increased dramatically during the 1970s, but then waned just as quickly during the 1990s. These rapid shifts in prescribing patterns were not strongly evidence-based because large multicenter trials to evaluate clinical outcomes were never done.

Despite the widespread use of theophylline in the past, Barr and colleagues could identify only 4 trials of reasonable quality that assessed it as a treatment for COPD exacerbations. These 4 trials altogether enrolled only 169 patients. The lack of a standard protocol made it difficult to pool estimates for most outcomes. Overall, scant evidence exists that theophylline had any beneficial effect, but because of the small numbers of patients studied, clinically meaningful improvements might have been missed. Even if it confers some benefit, theophylline is probably a poor choice for treating acute COPD exacerbations because of the frequency of nausea and vomiting.

Does this mean that we have heard the last of theophylline? Not necessarily. New findings suggest that theophylline may possess anti-

inflammatory effects at levels below those clinically used in the past (1). Moreover, secondary results from 2 large trials of stable COPD show that theophylline may prevent severe COPD exacerbations when given long term (2, 3). If these findings can be confirmed, theophylline might yet play an important role in the treatment of COPD, if not for treating exacerbations, then for their prevention. The low cost of generic theophylline might make it attractive for the treatment of stable COPD.

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