

EBEM Commentator
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Addition of Intravenous
Aminophylline to β_2 -
Agonist in Adults With
Acute Asthma

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SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to β_2 -agonists in adults with acute asthma (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford, United Kingdom: Update Software; 2002.

The *Annals'* EBEM editors prepared the abstract of this Cochrane systematic review as well as the Evidence-Based Medicine Teaching Points.

OBJECTIVE

To determine whether intravenous aminophylline is an effective treat-

ment for acute asthma in adults presenting to the emergency department.

DATA SOURCES

Studies were identified by searching the Cochrane Airways Group register (derived from regular standardized searches of MEDLINE, EMBASE, CINAHL, hand-searched respiratory journals, and meeting abstracts). The bibliographies of potentially relevant articles were hand searched for additional citations. The review is updated to June 2000.

STUDY SELECTION

Published and unpublished studies in any language were reviewed by independent reviewers and included if they were randomized controlled trials that assessed the use of β -adrenergic agonists plus intravenous aminophylline to β -adrenergic agonists plus placebo in adults with acute asthma attending EDs or other acute care settings. Patients could receive corticosteroids or other bronchodilators. Studies involving only children, patients with chronic obstructive pulmonary disease, patients requiring mechanical ventilation, or patients who were admitted for more than 24 hours were excluded.

DATA EXTRACTION

Data were extracted, entered into Review Manager (version 4.0), and double-checked by 2 reviewers. Some data were estimated from graphs. Results are reported as weighted mean differences (WMD) or odds ratios (OR), both with 95% confidence intervals (CIs).

MAIN RESULTS

Fifteen trials involving 739 patients aged 15 to 60 years were included in this review. The overall methodologic quality was moderate; concealment of allocation was “clear” in 7 (45%) trials. The dose range of aminophylline and other medications and the baseline severity of asthma varied. Meta-analysis showed no statistically significant differences in peak expiratory flow rate (PEFR) or FEV₁ between aminophylline and placebo at any time period. The small differences observed would not be considered clinically important. At 1 hour posttreatment, the aminophylline group had similar values to the control group for both PEFR (WMD -6.2 L/min; 95% CI -34 to 21; WMD 1.5% predicted; 95% CI -1 to 4) and FEV₁ (WMD 0.0 L; 95% CI -0.2 to 0.1; WMD 3.0% predicted; 95% CI -7 to 13). At 12 hours posttreatment, differences were PEFR (WMD -8.3 L/min; 95% CI -37 to 21; WMD -2.2% predicted; 95% CI -10 to 6) and FEV₁ (WMD -0.4 L; 95% CI -1 to 0.2; WMD -4.3% predicted; 95% CI -26 to 18). Nor were there significant differences at 24 hours. Two subgroup analyses, performed according to mean baseline airflow limitation (n=7 severe/4 mild-moderate) and use of steroids (n=6 yes/3 no) showed no differences. Patients treated with aminophylline reported more palpitations/arrhythmias (OR 2.9; 95% CI 1.5 to 5.7) and vomiting (OR 4.2; 95%

CI 2.4 to 7.4) but no difference in tremor or hospital admissions.

CONCLUSIONS

The use of intravenous aminophylline does not result in any additional bronchodilation compared with standard care with β -agonists. No subgroups in which aminophylline might be more effective could be identified. The frequency of adverse effects was higher in the aminophylline group. These results should be added to consensus statements and guidelines.

Cochrane Systematic Review
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COMMENTARY: CLINICAL
IMPLICATION

Since a landmark meta-analysis in 1988 suggested there was no advantage to adding intravenous aminophylline to inhaled β -agonist therapy,¹ the use of this agent as a routine agent for the treatment of acute asthma in adults has declined. In contrast, children presenting with acute asthma appear to benefit marginally from this strategy.² Subsequent studies in adults have confirmed both the lack of measurable benefits and the higher frequency of adverse effects—findings that make it hard to justify the significant time and effort needed to administer and monitor the drug.

Whether or not aminophylline may be useful as an “nth-line” agent in adult acute asthma is unclear. Life-

threatening acute asthma is uncommon, and data on patients who have received aminophylline *after* treatment with proven medications—inhaled β -agonists, systemic corticosteroids, inhaled ipratropium bromide, and intravenous magnesium—are sparse. Many of the drug’s beneficial effects occur only after hours of treatment (hence the benefits in chronic persistent asthma), but studies in severe acute asthma have typically reported only short-term outcomes (ie, in-ED and 24-hour PEFR or FEV₁ changes, hospital admission rate). In this subset of patients, even a small benefit may be clinically important in the fight to stave off respiratory failure and intubation. Only large-scale, well-designed, multicenter clinical trials may be able to establish definitively whether the agent should play any role in acute asthma management in adults. Given the alternative medications currently available, the relatively rare nature of this type of presentation, and the complexity of the intervention, such a study is unlikely to be conducted.

In the meantime, the current systematic review combines an extensive search strategy with a rigorous study-quality assessment to provide a focused update with a clear message: aminophylline should not be used in the routine care of adults with acute asthma.

TAKE HOME MESSAGE

The use of intravenous aminophylline as a routine agent for the treatment of acute asthma in adults has declined in the past decade, but its role in management of severe acute asthma remains unclear. This review fails to provide definitive evidence of benefit, especially in severe asthma. Conversely, the authors identify clear evidence of harmful

side effects. In summary, aminophylline should not be used in adults with acute asthma.

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review has been identified in a specific topic area.

REFERENCES

1. Littenberg B. Aminophylline treatment in severe, acute asthma: a meta-analysis. *JAMA*. 1988;259:1678-1684.
2. Mitra A, Bassler D, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over 2 years using inhaled bronchodilators (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford, United Kingdom: Update Software; 2002.

EVIDENCE-BASED MEDICINE TEACHING POINTS

Weighted mean difference. This method of meta-analysis combines measures of continuous variables (such as weight or peak flow rate), for which the mean, standard deviation, and sample size in each group are known. Each study's "weight" or influence on the overall results of the meta-analysis is determined by the precision of its estimate of effect (ie, the inverse of the variance). This method assumes that all of the trials have measured the outcome on the same scale.

Central. The Cochrane Collaboration's specialized register of controlled clinical trials and randomized controlled trials is also referred to as the Cochrane Controlled Trials Register (CCTR). This database is maintained and updated by the New England Cochrane Center, Providence Office. It was created through structured searches of MEDLINE and other sources and by contributions from Cochrane Review Group registers and hand-searching efforts. Currently, it is the most comprehensive collection of controlled clinical trials available and is often examined by authors to ensure that comprehensiveness in trial searching has been achieved. Clinicians may also conveniently use this resource to search for trials when no systematic