Theophylline in acute childhood asthma: a meta-analysis of its efficacy

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Authors' objectives
To determine the efficacy of theophylline in children hospitalised with acute asthma.

Searching
MEDLINE was searched from 1966 to May 1994; details of the search strategy were given.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) with study durations ranging from 24 to 36 hours, and until discharge, were included.

Specific interventions included in the review
IV Aminophylline or IV theophylline in the context of standard therapy for asthma, i.e. the treatment groups also received other bronchodilators and steroids, while the comparison groups received the same standard therapy, with the omission of theophylline.

Participants included in the review
Children hospitalised with acute asthma. Overall, the included patients were aged 1.5 to 18 years. Mean ages reported by the included trials ranged from 7 to 12 years.

Outcomes assessed in the review
The outcomes reported by the individual studies were transformed into effect sizes, which expressed the difference in mean score between the treatment and comparison group in units of measurement. These outcomes varied from trial to trial, but included measures of forced expiratory volume (FEV), forced vital capacity (FVC), changes in clinical scores, respiratory and pulse rates, duration of hospital stay, and need for albuterol nebulisations. Information on adverse effects was not extracted from studies as the focus of the review was on efficacy.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of the individual trials was not fully assessed, though all trials are described as randomised and double-blinded. The power of each individual study was assessed by calculation of required sample sizes for each outcome. The authors do not state how the papers were assessed for quality, or how many of the authors performed the quality assessment.

Data extraction
All data on study methodology and results were abstracted by one author.

Methods of synthesis
How were the studies combined?
An effect size was calculated for each reported outcome, representing the difference between treatment and comparison group in mean or median value. A pooled effect size was calculated using the methods of Light and Pillemer (see Other Publications of Related Interest). There was no weighting of studies by any measure of quality.
How were differences between studies investigated?
A chi-squared test was used to examine heterogeneity; it was not significant.

Results of the review
Six trials with a total of 164 patients were included.

The pooled effect size of the 24 hour spirometry measure (FEV or peak expiratory flow rate) showed a greater improvement in the theophylline group, though the difference was not significant (pooled effect size: 1.6 standard deviation, SD units; 95% confidence interval, CI: -2.6, 5.9, p<0.25). For the number of albuterol treatments required, the pooled effect size was -0.18 SD units (95% CI: -0.3, -0.1, p=0.02), showing more treatments were needed in the theophylline group. The pooled effect size for hospital stay was -0.18 SD units (95% CI: -0.3, -0.05, p=0.03), corresponding to a longer hospital stay (0.31 days) for the theophylline group.

Authors’ conclusions
Currently available data do not indicate a significant beneficial effect of theophylline in children hospitalised with acute asthma. There is evidence for weak detrimental effects.

CRD commentary
The authors’ conclusions are broadly true, though the suggestion of weak detrimental effects is speculative. These effect sizes are very small and could be due to, e.g. differences in severity between treatment and comparison groups due to inadequate randomisation or other methodological weaknesses in the trials (e.g. lack of prospective, standardised assessment of adverse effects).

Implications of the review for practice and research
Research: The authors stated that there have been no published studies of theophylline effects in children with respiratory failure. Future studies should ensure that they are of adequate power to detect small effects. Future researchers should consider the generalisability of the study population; in particular, children aged under 5 years are under represented in existing trials, yet this is the group with the highest hospitalisation rate. Hospitalisation rate also varies with sex and race, and adequate representation of these patient groups in trials is important.

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Other publications of related interest

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