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Expert Commentary

Commentary on 'Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators'

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This is a commentary on a Cochrane review, published in this issue of EBCH, first published as: Mitta A, Bassler D, Goodman K, Lasserson TJ, Ducharme FM. Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators. *The Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD001276. DOI: 10.1002/14651858.CD001276.pub2.

Guidelines on treatment of acute severe asthma in children over two years of age consistently recommend inhaled bronchodilators along with systemic corticosteroids as first-line treatment in children presenting to hospital accident and emergency departments (1,2). These recommendations are based on high-quality evidence (i.e. systematic reviews and several randomized controlled trials). The choice of additional treatment in children who respond poorly to this initial therapy is less clear. Options to be considered include intravenous salbutamol, magnesium sulphate, or aminophylline (1). Mitra and coworkers performed a systematic review of studies comparing intravenous aminophylline to placebo in such patients (3).

The overall methodological quality of the RCTs in this systematic review was good, with a mean Jadad score of 4.7 (on a scale from 0 to 5). The results were consistent in all outcome parameters. The primary outcome parameter in the review was lung function. Compared to placebo, aminophylline improved forced expiratory volume in one second (FEV_1) during the first 6–24 h of treatment. The observed effects were both statistically significant and clinically relevant (weighted mean differences 8.4–8.9% of predicted). There was no effect of aminophylline on length of hospital stay (95% CI of difference between groups −9.45 to 5.25 days) or the number of bronchodilator treatments in the first 24 h (95% CI of difference between groups −0.52 to 0.83). Although data from a single study tended to favour aminophylline in reducing intensive care admission and mechanical ventilation rates, there was insufficient data to draw reliable conclusions on these outcomes.

There may be some concern regarding the generalizability of these results. All but one study in the review included patients who had received inhaled $\beta 2$ agonist therapy alone by nebulization. Currently, the preferred method of administration of inhaled $\beta 2$ agonists is by metered dose inhaler (MDI)/spacer combination (4). Given the fact that it has been shown that nebulized $\beta 2$ agonist therapy is as effective as $\beta 2$ agonists by MDI/spacer (it's just more expensive) (4), it is unlikely that this would cause an important difference in the size of the effect when MDI/spacer are used.

More importantly, there is good evidence from systematic reviews that the addition of ipratropium bromide to nebulized $\beta 2$ agonist therapy improves outcome in acute severe asthma in children (5). The easiest way to combine $\beta 2$ agonists and ipratropium bromide is by nebulization, and some authors prefer this route of administration for this purpose (6). In this systematic review, there was only one study including children being treated with both $\beta 2$ agonists and ipratropium bromide (7), which is the currently recommended treatment approach in acute severe asthma in children (1,4). Although this was a relatively large trial with 163 patients the generalizability of this particular trial is limited because it was performed in a single tertiary care referral centre, and almost half of the included patients were admitted to the paediatric intensive care unit. Therefore, this appears to be a highly selected group of patients with severe exacerbations.

Thus, although the methodological quality of the studies in the review is good, the generalizability is somewhat limited because the only study examining the patient group of interest (i.e. children not responding favourably to frequent nebulizations of $\beta 2$ agonist and ipratropium) included a selected group of children with severe disease.

In my view, the main reason to use aminophylline would be to try and prevent (referral to a tertiary care facility for) intensive care admission in children with acute severe asthma. This particular patient group has

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never been examined in clinical trials to date. This also questions the authors' choice to use lung function as the primary outcome measure. The clinical value of improving lung function during the first 24 h of treatment is limited in the absence of apparent effects on intensive care admission rates, mechanical ventilation rates, and length of hospital stay. In the only trial examining intensive care admission rates in this field, there were 30/81 admissions in the aminophylline group, compared to 41/82 in the placebo group (ARR 16%, NNT = 6) (7). In the same study, mechanical ventilation rates were difficult to study because most of these patients (9/14) had been intubated prior to randomization. If one compared intubation rates in the two groups in an intention-to-treat fashion, this trial found 3/81 intubations in the aminophylline group and 11/82 in the placebo group (ARR 9.7%, NNT = 10).

As pointed out by the authors of the present systematic review, large, preferably multicentre trials are needed to compare aminophylline to placebo in children with acute severe asthma who do not respond favourably to initial therapy with systemic corticosteroids and both nebulized $\beta 2$ agonists and ipratropium bromide. In addition, head-to-head comparisons of different treatment options in such patients (comparing, e.g. intravenous aminophylline, magnesium sulphate, and salbutamol) should be carried out. In one such study, hospital stay was 1 day shorter in children treated with aminophylline as compared to iv salbutamol (8).

In conclusion, there is moderately good evidence to suggest that aminophylline improves lung function in the first 24 h of treatment in children with acute severe asthma already receiving systemic corticosteroids and inhaled $\beta 2$ agonists. Because there is no good evidence on the effects of different treatment options in children responding unfavourably to systemic corticosteroids, inhaled $\beta 2$ agonists *and* ipratropium, clinicians will have to rely on personal judgement and experience in this difficult patient category. Until results from large RCTs become available.

Response

Francine Ducharme

Thank you for giving me the opportunity to comment on these high-quality documents and commentary.

I have a couple of comments on Dr Brand's commentary. In answer to his criticism about generalizability, I think it is important to highlight the type of patients enrolled in the trials. In six of the seven trials, patients were recruited in the emergency department after displaying poor response to two to three maximised doses of salbutamol and to oral steroids; that is, enrolled patients had a persistent severe airway obstruction with forced expiratory volume in 1 sec (FEV1) of less than 50% of predicted, when measured. Clearly this is the type of patients for whom one would consider adding aminophylline and hopefully prevent an intensive care unit admission.

The addition of ipratropium bromide to inhaled salbutamol is clearly beneficial in these severe patients; it constitutes the gold standard therapy for the initial management of acute severe asthma. However, we must acknowledge that the efficacy of anticholinergics appears to be limited to the initial 4 h of treatment, i.e. before the effect of oral steroids become evident. Indeed, two trials conducted in hospitalized children have failed to show any benefit of anticholinergics as add-on to $\beta 2$-agonists and oral steroids compared to $\beta 2$-agonists and oral steroids alone. While ideally we would have preferred pooling trials testing aminophylline as add-on to maximised $\beta 2$-agonists, anticholinergics, and oral steroids, the lack of treatment with anticholinergics does not negate the efficacy of aminophylline observed after 6 h of treatment and beyond.

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