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Viewpoint

Treating acute severe asthma attacks in children: using aminophylline

Introduction

A child with an acute attack of asthma is a well-recognised clinical presentation amongst acute-care clinicians. In those children who do not respond adequately to first-line treatment of inhaled bronchodilators and oral steroids, second-line intravenous bronchodilator therapy is usually commenced. In the authors' clinical experience, there are extreme views on one of the *i.v.* drugs of choice: aminophylline. There is a weak evidence base, and the decision of which drug to use is often simply based on the personal choice of the clinician and local accepted practice and guidelines. When aminophylline is suggested, polarising views are expressed: "it is dangerous and unsafe"; "it is the devil's poison"; and "it should be removed from the shelves of the emergency department (ED)". Other clinicians feel it is the only useful *i.v.* treatment in severe acute attacks. This narrative review aims to consider the use of aminophylline in treating severe asthma attacks in children.

Treatment of acute attacks of asthma in children

Asthma is one of the most frequently encountered problems in clinical practice [1, 2]. The first-line therapy for childhood asthma attacks is the same worldwide with inhaled β_2-agonists, high-flow oxygen and oral steroids. Second-line management policies vary according to geographical location [1–6]. In a study examining the management of acute attacks in the UK and the Republic of Ireland, aminophylline was used in 47.3% of cases, magnesium sulphate in 60.9% and salbutamol in 55.5% [7, 8].

The British Thoracic Society (BTS) recommends an aminophylline loading dose of 5 mg·kg^{-1} followed by an infusion [2]. The Global Initiative for Asthma (GINA) and the US National Institutes of Health (NIH) does not recommend its use at all, stating that it should not be used due to poor efficacy and a safety profile with potentially fatal side-effects [3, 4]. Previously, a study from Australia showed aminophylline, with a loading dose of 10 mg·kg^{-1} compared with placebo and standard treatment, showed significant improvement in physiological recovery and reduced intubation rates despite the side-effects like nausea and vomiting [9, 10]. Subsequently, aminophylline is recommended at a loading dose of 10 mg·kg^{-1} in some children's hospitals in Australia and New Zealand [11, 12]. The adverse effects of aminophylline should undoubtedly be considered, but does this mean that its use should be stopped completely?

Pharmacological actions of theophyllines

Aminophylline is a methylxanthine bronchodilator composed of theophylline and ethylenediamine. Theophylline relaxes the smooth muscle of the

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Aminophylline does have a role in treating severe asthma attacks in children with asthma. Clinicians just need to be aware of the toxic side-effects of the drug and manage the drug carefully.
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bronchial airways and pulmonary blood vessels as well as reducing airway responsiveness to histamine, methacholine, adenosine and other chemical mediators. They also competitively degrade type III and IV phosphodiesterase. These are the enzymes responsible for the degradation of cAMP in smooth muscle cells resulting in bronchodilation. They also may block adenosine receptors, thus inducing bronchodilatory adrenergic action, and there is a suggestion of an anti-inflammatory action through reducing eosinophil and neutrophil numbers [13]. Aminophylline has a narrow therapeutic range, and toxicity and side-effects need to be considered [10].

What does history tell us?

Of course, like all other drugs, theophyllines are toxic when given at certain doses in both children and adults. One of the first reports on the dangers of theophyllines was published in 1957 [14]. A 3-year-old child with acute asthma died after a 32 $mg \cdot kg^{-1}$ dose of aminophylline, repeated three times in 24 h, was administered rectally. They then went on to review 35 children in their institution who had toxicity and reported seven (20%) deaths, 14 (40%) instances of seizures and 33 (95%) cases of vomiting. The doses used in the 35 children ranged from 9 to 62 $mg \cdot kg^{-1}$ repeated every 3 to 12 h. These were massive doses compared with the current recommended guidelines. Interestingly, they concluded that the therapeutic dose in children had not been determined. Still, from the author's clinical experience, safe yet effective individual doses range from 3 $mg \cdot kg^{-1}$ intravenously to 7 $mg \cdot kg^{-1}$ rectally, repeated at intervals of 6 to 12 h. Finally, they concluded that "The purpose of the paper is not to condemn the use of aminophylline in children, but to advise care in selecting the dose, to bring about awareness of early symptoms of toxicity and to urge that such medications be kept out of the reach of young children". This continues to be the case and should be the main conclusion of this paper [15, 16].

Does aminophylline work in children?

Efficacy of aminophylline depends on dosing and toxicity. In the adult literature, a Cochrane review from 2012 recommends that aminophylline should not be considered for use in acute asthma due to serious side-effects and limited efficacy [17]. So, what does the literature tell us about the recommended dosing and efficacy and safety of aminophylline in acute childhood asthma?

Methodology

We conducted a literature search in major databases, such as MEDLINE, EMBASE, CINAHL, Web of Science and the Cochrane Central Register of Controlled Trials (CENTRAL), since inception of the databases until September 2020. The major search concepts used were "asthma", "acute exacerbation", "child" and "aminophylline". This is a narrative review based on 13 recent papers (table 1) [5, 7, 8, 10, 13, 18–25].

Results

Is aminopylline safe?

The most recent systematic review by Mahemuti *et al*. [18] examined combined adult and paediatric data from 52 study arms in 42 individual trials. In all these study arms, 29 compared aminophylline to an active control (such as adrenaline, β2 agonists and leukotriene antagonists) while 23 studies compared it to placebo. Although they did not make a specific comment about the quality of the evidence, very few of these studies had a high risk of bias, and there was no evidence of publication bias. They concluded that aminophylline had similar efficacy and rate of side-effects compared with other drugs when given with bronchodilators; indeed, no deaths were reported in any of these studies [18]. Of course, the devil is in the detail. Nausea and vomiting were higher in the aminophylline group compared with placebo (odds ratio for nausea 6.05 (95% CI 3.65–10.38) and for vomiting 5.35 (95% CI 3.14–9.12)). Other noted side-effects included palpitations, tachycardia and arrhythmias in the aminophylline group (odds ratio 3.52 (95% CI 1.66–7.49)), but this was only reported in the adult studies.

In the study arms comparing aminophylline with other active treatments, nausea and vomiting were more likely in the aminophylline group. However, there were no differences reported for psychological problems, headaches, abdominal pain, cardiovascular issues, seizures, creatine phosphokinase/creatine kinase elevation, hyperglycaemia and tremors. Overall, aminophylline showed a significant reduction of heart rate (p=0.01) and length of hospital stay (p=0.002) when compared with active controls. In adult studies, *i.v.* β_2-agonists showed improved lung function compared with aminophylline. There was no difference in symptom score, oxygen saturation and use of rescue medication or admission rate. Therefore, the overall evidence suggests that aminophylline has a similar efficacy to other treatments. They attempted to do a subgroup analysis based on age but the only factor they could compare directly was symptom improvement. There were no differences between adult and paediatric studies with both arms showing improved symptoms compared with active controls [18].

Dosing of aminophylline

Cooney *et al.* [10] completed a useful systematic review on aminophylline use in children with acute

Table 1 *Studies in the past 5 years concerning use of aminophylline in children with acute severe asthma*

First authors [ref.], year	Type	Methods	Findings of the study	Conclusion and comments
Indinnimeo *et al.* [5], 2018	Guideline	The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology was agreed. Used Cochrane library and Medline/PubMed databases for literature search, and including children over 2 years of age.	Aminophylline use should be avoided in mild to moderate attacks. Moreover, weak clinical evidence supports its use in life-threatening attacks.	This guideline emphasises that few studies are available regarding the use of a low dose of aminophylline, but then again, further data is needed regarding this issue.
Morris *et al.* [7], 2015	Audit, research and guideline update	A prospective observational multicentre study in the UK and Ireland.	3238 children aged 1–16 years presented with acute wheeze over a 10-week period. In those receiving *i.v.* bronchodilators, *i.v.* magnesium sulphate ($MgSO_4$) was used in 67 (60.9%), salbutamol in 61 (55.5%) and aminophylline in 52 (47.3%) of cases. The most common aminophylline regimen was a load followed by an infusion.	Authors point at the inadequate evidence in significant areas of childhood wheeze and emphasise the need for further robust multicentre research studies.
Lyttle *et al.* [8], 2015	Cross sectional observational study examining current practice across the UK and Ireland	Survey study involving physicians in the UK and Ireland.	Variation exists in the treatment of acute severe childhood wheeze, especially in inhaled and *i.v.* bronchodilator selection, dosage and frequency. Aminophylline is the third most commonly used medication, Salbutamol is first, and $MgSO_4$ is second. Authors identified strategic areas of variation, which require further exploration to determine their impact on the patient interface.	Despite the presence of national guidance, there is a significant discrepancy in managing childhood asthma from physicians.
Cooney *et al.* [10], 2016	A systematic review	Systematic review compared dosage regimens of *i.v.* aminophylline in children suffering an exacerbation of asthma.	In this review, 14 RCTs were included and it concluded that there is a weak relationship between the dosage administered to children and symptom resolution, length of stay or need for mechanical ventilation.	The currently recommended dosage regimens may not symbolise the optimum safety and efficacy of *i.v.* aminophylline. There is a need to improve the evidence base correlating dosage with patient-centred clinical outcomes, to improve prescribing practices.

(*Continued*)

Table 1 Continued *Studies in the past 5 years concerning use of aminophylline in children with acute severe asthma*

First authors [ref.], year	Type	Methods	Findings of the study	Conclusion and comments
Saint *et al.* [13], 2018	Current opinion	Review of the literature.	Review assessing the evidence underpinning use of aminophylline in acute asthma, its recommendations, highlighting the shortcomings in the understanding of the association between serum concentrations achieved, the dose is given, and clinical improvement experienced.	The dosing regimen with aminophylline in the management of acute severe asthma is minimally evidenced. Cluster and standardised prospective studies are required.
Mahemuti *et al.* [18], 2018	A systematic review and meta-analysis	In this review, 52 study arms were included that compared theophylline with other drugs, like adrenaline, β_2- agonists or leukotriene receptor antagonists, or placebo.	Theophylline significantly reduced heart rate when compared with active control (p=0.01) and overall duration of stay (p=0.002), but β_2-agonists were superior to theophylline at improving FEV_1 (p=0.002). Theophylline was not significantly different from other drugs in its effects on respiratory rate, forced vital capacity (FVC), peak expiratory flow rate, admission rate, use of rescue medication, oxygen saturation, or symptom score. When other intravenous bronchodilators are given in addition to theophylline, this significantly improves the effectiveness of theophylline (subgroup difference: p<0.00001). Most notable side-effects were nausea and vomiting.	This evidence shows that *i.v.* theophylline is superior to other treatments with regard to heart rate and duration of hospital stay. Authors feel that given the small cost and similar safety profile, theophylline should be considered as a cost-effective treatment for acute asthma exacerbations. Considering this evidence, it is useful, especially for developing countries with restricted health budgets.
Cooney *et al.* [19], 2017	A prospective study, single centred	Prospective clinical audit of children receiving *i.v.* aminophylline, and *in-silico* modelling using Simcyp software.	Aminophylline was used with a loading dose of 5 $mg \cdot kg^{-1}$ over 20 min and found that resulted in a serum concentration of <10 $mg \cdot L^{-1}$ in 70.3% of cases, 10–20 $mg \cdot L^{-1}$ in 29.4%, and >20 $mg \cdot L^{-1}$ in only 0.1% of cases who receive it. Nevertheless, almost all cases achieved a serum concentration of 5–15 $mg \cdot L^{-1}$ using this loading dose.	Used only one loading dose and need to have more information about efficacy when used other loading doses like 10 $mg \cdot kg^{-1}$ loading dose? There is still doubt that serum level is sub-optimal, the dose incorrect, or both?
Eid *et al.* [20], 2016	Retrospective study	Authors used low-dose theophylline (5–7 $mg \cdot kg^{-1} \cdot day^{-1}$) in addition to the current standard of treatment for children with acute asthma.	57 children are included in the low-dose theophylline group and 109 in the control group. Theophylline significantly reduces LOS, time to discontinue oxygen, time to spirometric improvement and time to space salbutamol, as well as reduced costs. Moreover, there is no significant difference in adverse effects between patients who receive low-dose theophylline and those who did not.	Authors' opinion is low-dose and oral theophylline may have a positive effect on acute status asthmaticus.

(*Continued*)

Table 1 Continued *Studies in the past 5 years concerning use of aminophylline in children with acute severe asthma*

First authors [ref.], year	Type	Methods	Findings of the study	Conclusion and comments
Neame *et al.* [21], 2015	Review- pharmacy update	Review of RCTs and Cochrane reviews comparing salbutamol and aminophylline.	Both drugs have proven use in treating acute asthma. Both drugs have shown similar results. The variance of practice at individual clinician and departmental level is likely to continue with regards which of these agents should be used first.	The choice of the first drug is based on the risk management considerations such as easiness of prescription, preparation and administration factors and availability of resources like high-dependency beds. This qualitative analysis failed to draw any conclusions due to "minimal and inconsistent" evidence.
Singhi *et al.* [22], 2014	RCT, prospective study	This study compared the effectiveness of *i.v.* $MgSO_4$, terbutaline and aminophylline for children as the second line of treatment in acute severe asthma.	The $MgSO_4$ group had significant treatment success (97%) compared with the terbutaline and aminophylline groups (70%) and quicker resolution of retractions, wheeze and dyspnoea.	Recommends using $MgSO_4$ as the second line of medication but needs a multicentre study. The sample size was small (100), and the age range of the participants includes very young children.
Castro-Rodriguez *et al.* [23] 2015	Systematic reviews of RCTs with or without meta-analysis in children (1–18 years)	A limited review of the use of aminophylline in children with acute asthma and included a Cochrane review which included both children and adults.	There is no consistent evidence favouring either *i.v.* β_2-agonists or *i.v.* aminophylline for patients with acute asthma.	The opportunity to draw definite conclusions is limited by the heterogeneity of outcomes evaluated and the small sample sizes in the included studies.
Tiwari *et al.* [24] 2016	RCT	Single centre study involving children from 1–12-years age group. It randomised 24 patients each in ketamine and aminophylline groups. The primary outcome was the PRAM score.	Both ketamine and aminophylline were equally effective for children with acute asthma who responded poorly to standard therapy.	Authors have used objective scoring to assess the outcome but limited in numbers of patients. May not be applicable in all settings as a need for intensive care support.
Albertson *et al.* [25] 2015	The clinical review includes adults and children	A comprehensive summary is provided concerning the currently available drugs approved for asthma.	The use of theophylline in the treatment of acute asthma is limited because of both the lack of supportive data and significant adverse effects associated with its use.	Authors conclude that there is no clear consensus in using theophylline dosage, administration, or preference.

RCT: randomised controlled trial; LOS: length of stay; PRAM: Pediatric Respiratory Assessment Measure.

asthma. This review focused on 14 randomised controlled studies in children with a focus on dosage of aminophylline. First, there were no reported deaths in any studies. They highlighted that when the loading dose of 7–10 mg·kg^{-1} is given, this is associated with nausea and vomiting. When lower dosages are used (5–6 mg·kg^{-1}), this is not associated with nausea and vomiting. No studies compared side-effects between β_2-agonists and aminophylline. Time to resolution of symptoms does not appear to be related to the magnitude of the loading dose of aminophylline. None of the studies reported evidence supporting the 1998 study that showed the use of aminophylline, compared with placebo, reduced the likelihood of being intubated and admitted to intensive care [9]. Length of stay was shorter in those children who received aminophylline (loading dose of 5 mg·kg^{-1} and infusion of 0.9 mg·kg^{-1}·h^{-1}) compared with β_2-agonists. Still, when other studies were examined, there was no difference in asthma score, time until discharge and length of stay. Their conclusions were that there is a poor relationship between dosage and patient-centred outcomes [10]. This group went on to look at the optimal paediatric dose in acute asthma. They concluded that a loading dose of 5 mg·kg^{-1} does not achieve what is considered to be the therapeutic range expected by clinicians in most patients. The clinical evidence that the therapeutic range of 10–20 mg·L^{-1} is associated with improved clinical outcomes in severe attacks of asthma is limited [13]. More pharmacokinetic studies are required to answer these questions before larger multicentre studies are completed comparing the efficacy of the four currently used *i.v.* bronchodilators [19]. So, there is a lack of evidence on the most effective dosage of aminophylline to use in children. Perhaps dosage greater than 7 mg·kg^{-1} may increase the rate of nausea and vomiting, but there was no evidence to show that dose adjustment using theophylline levels increases efficacy or safety of *i.v.* aminophylline [10, 13, 19].

There are no recent data to show that using aminophylline is dangerous and unsafe in children; no deaths have been reported in the paediatric population associated with the use of aminophylline. In these recent studies, there is no evidence that there is an increased risk of seizures or dysrhythmias in paediatric studies which use aminophylline in accepted doses. The main risk is that at higher loading doses (7–10 mg·kg^{-1}) there is an increased risk of nausea and vomiting.

It is interesting that at lower serum concentrations, aminophylline may act as an immunomodulant by exercising an inhibitory effect on T-lymphocytes in the airway of asthmatic patients, encouraging neutrophil apoptosis and lowering inflammatory gene expression. Also, theophylline may prevent downregulation of β-receptors by β_2-agonists. One of the essential anti-inflammatory properties of aminophylline is the ability to restore histone deacetylase-2 activity, which leads to enhanced steroid responsiveness. A retrospective, observational study design showed that adding low-dose theophylline to children with severe attacks of asthma may positively affect clinical parameters, shorten hospital stay, and decrease overall healthcare costs. This study recommended that low-dose theophylline may have a positive effect on acute *status asthmaticus* [20]. The target therapeutic range for aminophylline in children has a generally accepted range of 10–20 mg·L^{-1}. The target serum concentration of aminophylline is challenging to achieve, as it is complicated by its high interindividual variation in clearance rates. The reasons for interindividual variation are not known, though it has been postulated that various factors like age, weight and previous serum drug level play a role. The current recommended dosage of *i.v.* aminophylline in childhood asthma exacerbations might not exemplify the optimum safe and adequate serum drug level [10, 13, 15]. Aminophylline's effects as a bronchodilator have made it a backbone therapy for inpatient asthma management for decades in some centres and it still is the backbone in many today [9, 10]. However, given the potential toxicity and unclear clinical effectiveness, the *i.v.* formulation of aminophylline has fallen out of favour with the rise of selective β-agonists, and its use is currently discouraged by some asthma guidelines [3, 4].

Aminophylline *versus* placebo

A 2005 Cochrane review showed that children with acute severe asthma treated with aminophylline had an improvement in lung function compared with the placebo group [26]. The addition of aminophylline to steroids and β_2-agonist significantly improved forced expiratory volume in 1 s (FEV_1) % predicted over placebo at 6–8 h, 12–18 h and 24 h; and aminophylline led to a greater improvement in peak expiratory flow % predicted over placebo at 12–18 h. However, the addition of aminophylline was not associated with a significant reduction in the number of nebulised bronchodilator treatments and length of hospital stay. The review also mentioned that aminophylline use resulted in a higher risk of vomiting. There is insufficient evidence to confirm the use of aminophylline in children with severe acute attacks of asthma. However, the authors urged for high-quality trials to compare the clinical effectiveness of aminophylline with other drugs, given promising results in smaller trials [26].

Aminophylline *versus* β_2-agonists

Another Cochrane review in 2012 based on adults did not support the use of aminophylline in acute asthma [17]. This review revealed that there is no significant additional bronchodilation compared with standard care with inhaled β_2-agonists.

The side-effects were significantly higher in the aminophylline group compared with the β_2-agonist

group, as the aminophylline group had more chance of vomiting (20/100), palpitation (15/100) and arrhythmia (15/100). This update concluded that the risk–benefit balance of *i.v.* aminophylline is unfavourable [17].

Neame *et al*. [21] examined in detail the difference between β_2-agonists and aminophylline at the second tier of treatment in children. The evidence of efficacy from all the published randomised controlled studies for either of the two drugs is minimal and inconsistent. There is inconsistency in study design, definitions, primary outcomes, dosage and regimens used, interventions and comparisons and reporting of side-effects. Along with the varying quality of evidence and risk of bias, it is impossible to make any firm conclusions. However, they conclude that aminophylline may improve symptoms, reduce the length of stay and improve lung function. Similarly, a bolus of β_2-agonists may also reduce symptoms and hasten recovery [21]. There is no clear evidence that either of these two drugs is superior in efficacy.

Travers *et al*. [27] found no significant differences in terms of hospital stay, peak expiratory flow rate, FEV_1, heart rate or clinical failure between *i.v.* β_2-agonists and *i.v.* aminophylline added to standard treatment. Thus, this review is not able to favour either of these two treatments.

Aminophylline *versus* magnesium sulphate

Singhi *et al*. [22] carried out a randomised controlled study involving 100 children aged between 1 and 12 years. The aim was to examine the efficacy of *i.v.* magnesium sulphate, aminophylline and terbutaline. Results revealed a higher success rate in children with magnesium sulphate than the terbutaline and aminophylline groups. They reported that adding *i.v.* magnesium sulphate was more effective and safer than using aminophylline alone when treating a child with acute, severe asthma poorly responsive to initial treatment. They reported faster resolution of retractions, wheeze and dyspnoea in the magnesium sulphate group. Furthermore, the aminophylline group had more side-effects like nausea and vomiting [22].

A further systematic review by Castro-Rodriguez *et al*. [23] concluded that aminophylline is not superior to other drugs like short-acting β_2-agonists, ketamine or magnesium sulphate. In this systematic review, *i.v.* magnesium sulphate resulted in fewer admissions to the ward when used in emergency settings. However, there is no robust evidence to conclude or guide the choice of second-line medications [23].

Aminophylline *versus* ketamine

In the only single centre, randomised controlled study examining *i.v.* aminophylline compared with *i.v.* ketamine the conclusion was that both are equally effective. Nevertheless, the study had a low power, in which there 24 cases in each group. This is likely to change, as the use of ketamine as second-line treatment could increase in the future for children who are refractory to conventional treatment, thus giving more opportunities for higher power studies [24].

Discussion

There are no recent data to show that using aminophylline is dangerous and not safe in children. Most importantly, no deaths have been reported in the paediatric population due to the use of aminophylline. There is also no evidence of an increased risk of seizures or dysrhythmias in the paediatric population with accepted doses of aminophylline. Intravenous aminophylline should not be considered for children with mild-to-moderate acute asthma, but it should be considered for use in severe acute asthma in children not responding to inhaled β_2-agonists and oral corticosteroids. The *i.v.* infusions of aminophylline may improve lung function, and some reviews have shown an improvement in signs and symptoms, but the evidence is minimal. Neame *et al*. summarise this issue well [18, 21]. The decisions about which treatment to use should include risk management considerations such as ease of prescription, preparation and administration factors, and availability of high-dependency beds. Whichever therapy is used, children should be assessed for objective markers of improvement of clinical status after the initial loading dose, to evaluate whether they need to be treated with a subsequent infusion or not. It is important to stress the importance of stringent and routine monitoring of the adverse effects. Another interesting conclusion from Mahemuti *et al*. [18] is that with the safety profile and low cost of aminophylline it must be regarded as a cost-effective treatment for acute asthma exacerbations, especially for settings of restrained health economy like in developing countries.

There is no evidence to suggest a safe and effective *i.v.* dosage of aminophylline for children with acute asthma. The recommended *i.v.* dose of aminophylline may not represent the optimum safety and efficacy profile. This is a crucial reason to limit to its use in children as there is insufficient evidence that dosage adjustments based on age, weight and previous serum theophylline levels improve asthma outcomes [10]. Mahemuti *et al*. [18] reported that combining *i.v.* aminophylline (theophylline) with other medications, like bronchodilators with or without steroids, is superior when compared with other treatments alone. The review mentioned that aminophylline caused significantly reduced heart rate and overall duration of stay. However, β_2-agonists were superior to theophylline at improving FEV_1. In this systematic

review, the authors felt that, given the low cost of treatment and restricted budget constraints, it could be considered as a cost-effective treatment for acute asthma [18].

To paraphrase the conclusion from the 1957 paper by McKee *et al.* [14], we believe that we should not condemn the use of aminophylline in children. Nevertheless, we do advise care in selecting loading dose and infusion rate. We do not believe that aminophylline should be taken off the shelves and believe it does have a beneficial role in severe exacerbations of childhood asthma. We have found that in current doses used in children, there is no firm evidence that the use of aminophylline is associated with death, palpitations, dysrhythmia and seizure in children. Nevertheless, clinicians need to be aware of the significant possibilities of toxicity, just like in any other pharmacological medication used in the clinical world [25]. The main concern is that of vomiting or nausea at high loading doses (7–10 $mg \cdot kg^{-1}$ over 20 min), which can be treated using anti-emetics. The use of anti-emetics along with aminophylline should, however, be studied in further detail. Lower loading doses (4–6 $mg \cdot kg^{-1}$ load over 30 min) are not associated with adverse side-effects. We believe that there is sufficient evidence of efficacy when compared to placebo or other *i.v.* bronchodilators to continue using it in our regimen. The evidence is weak, but we believe sufficient to support its use in children presenting to the emergency department with severe acute attacks. However, we need to promote the development of adequately powered studies using standard definitions of attacks and severity and have a worldwide-accepted set of core outcomes measured with patient- and family-centred outcomes [6]. We need to know more about the pharmacokinetics and therapeutic dose behaviour of aminophylline and other bronchodilators.

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Conflict of interest

None declared.

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