Optimising the dosing of intravenous theophylline in acute severe asthma in children

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Running Head:

Intravenous theophylline in the acute treatment of paediatric asthma

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# Abstract

Optimising the management of children presenting with acute severe asthma is of upmost importance to minimise hospital stays, morbidity and mortality. Intravenous medications, including theophyllines are used as a second line treatment for children experiencing a life-threatening exacerbation. For IV theophylline (aminophylline) guidelines and formularies recommend a target therapeutic range between 10-20mg/l with the commonest regime being a 5mg/kg loading dose, followed by an infusion calculated by age and weight. This review assesses the evidence underpinning these recommendations, highlighting the shortcomings in our understanding of the association between serum concentrations achieved, dose given, and clinical improvement experienced. In order to close the knowledge gap and improve outcomes for children presenting with acute severe asthma, a series of research strategies are proposed, to improve the assessment of illness severity, ascertain the optimal dose to maximise benefit and minimise risk, prospectively collect adverse events, and to better understand the inter-individual variation in responses to treatments.

Key Points

1. The aminophylline dose used for IV loading (5mg/kg) in UK and Eire does not achieve the therapeutic range expected by clinicians in the majority of patients.

2. There is limited clinical evidence that the target therapeutic range for aminophylline of 10-20mg/l improves meaningful clinical outcomes in severe asthma exacerbations.

3. Further pharmacokinetic work is needed in preparation for a clinically needed large three arm randomised controlled trial of intravenous bronchodilators in acute asthma

1. Background

The World Health Organisation estimates that 235 million people have asthma worldwide (1). It is the most common non-communicable disease among children. Annually, approximately 1 in 11 children in the UK receive treatment for an acute asthma exacerbation (1). The outcomes for children are worse in the UK than for many other similar countries, with higher mortality rates. Twenty five children died in 2015, and a child is admitted to a hospital every 20 minutes with acute asthma (1). There is an urgent clinical need to improve the morbidity and mortality associated with this condition.

In the UK, asthma is treated according to national guidelines produced by the British Thoracic Society (BTS)/Scottish Intercollegiate Guideline Network (SIGN) (2). First line therapy for children who present to an acute care setting with severe exacerbations involves frequent nebulised β2 agonists and ipratropium bromide driven by high flow oxygen, plus oral steroids. In the absence of a rapid improvement, or if life threatening features are present, then second-line intravenous (IV) therapies are considered.

Three IV options, magnesium sulphate, β2 agonists, and aminophylline are available. The BTS/SIGN guidance does not prioritise one drug over another. UK guidance differs from international guidance. In practice, all three IV treatments are frequently used in the UK and Ireland. Prospective data shows that, across a range of emergency departments, 3.3% (110/3238) paediatric asthma exacerbations required IV therapy (alone or in combination), of which magnesium sulphate was used in 60.9%, salbutamol in 55.5% and aminophylline in 47.3% of cases (3). Thirty different IV treatment regimens were used varying in drugs, dose, rate and duration.

The inclusion of aminophylline as a treatment for acute severe asthma varies across the world. The Global Initiative for Asthma (GINA) guidance, used in the USA, recommends for adults and children >5 years to receive a single bolus of magnesium sulphate only if escalating treatment is necessitated (4). The rationale for omitting aminophylline is that, based on a Cochrane review, it has limited efficacy and severe, potentially fatal, adverse effects. However, this review specifically excluded children from the analysis (5).

Tachycardia is a commonly reported side effect. In adults tachyarrhythmias have been reported but the frequency of such is not known within the paediatric population. Vomiting is also a commonly occurring adverse effect which can occur at all concentrations but more so at levels >20mg/l. Development of seizures have been reported in children, the mechanism and frequency of which are unknown.

Based on mechanism of action, aminophylline should be advantageous in asthma treatment. It is a methylxanthine bronchodilator composed of theophylline and ethylenediamine. Theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen. Theophylline competitively inhibits type III and type IV phosphodiesterase, the enzyme responsible for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation (6). Clinically there is evidence that patients with life-threatening asthma may benefit from IV aminophylline, but there is variability in the clinical outcomes reported (2, 7). This may in part be attributable to not achieving the desired therapeutic range or indeed that the targeted range may not be therapeutically optimal. This review will concentrate on the evidence underpinning the current dosing strategy, identify gaps in these data, and explore how future research can help to address these issues.

## 2. Current dosing of IV aminophylline

Aminophylline is believed to have a narrow therapeutic range and high inter-individual variation in clearance. In order to avoid toxicity UK and Eire clinicians have adopted a very consistent dosing strategy; the most commonly used loading dose is 5 mg/kg over 20–30 min, used in >95% of paediatric patients who received it (3). Therapeutic drug monitoring is also commonly used, with the aim of getting concentrations within the accepted therapeutic range of 10-20mg/L. This therapeutic range originated in the 1950s, when efficacy was only noted in a small cohort of adult patients (n=25) with chronic wheeze (8) at a concentration >10mg/L. Of note 20% of these patients had cardiac failure (8). Increased toxicity has been seen in individual studies with adults dosed to achieve 20mg/L compared with 10mg/L (9). There have been calls for alternate therapeutic ranges (e.g. 5-15mg/L) but this has not been translated into clinical practice in the UK (10).

It is not clear if this is the optimal therapeutic range, either in terms of benefit or risk. In a recent systematic review of ten RCTs and two observational studies, no evidence was found to support this therapeutic range (11). Children with serum levels between 10-20mg/l did not have any additional efficacy (i.e. reduction in duration of symptoms, length of hospital stay, need for mechanical ventilation, or improvement in spirometry) compared with levels <10mg/l (11). This is consistent with early studies on the effects of IV aminophylline where improvements in lung function were noted across a broader therapeutic range (5-20mg/l) (12). The systematic review also failed to show any differences in the frequency of adverse effects in children within the therapeutic range compared to those with levels above 20mg/l (11).

There is now significant evidence that the dose used for IV loading (5mg/kg) does not achieve the therapeutic range expected by clinicians in the majority of patients. This under dosing was initially predicted from the 1970’s pharmacokinetic (PK) work, which suggested that in children a 5.6mg/kg dose is required to achieve the target concentration of 10mg/L (13). Additional PK studies suggested 6mg/kg would be a more appropriate dose to achieve 10mg/L (14). However, these PK studies, whilst suggesting we under-dose for the therapeutic range we are targeting, do not provide clinical teams with any feel for the likelihood of any particular serum concentration, as the inter-individual variation is so large.

Higher loading doses have been used. One RCT demonstrated clinical benefits of aminophylline using 10 mg/kg, although delivered over 60 minutes rather than 20-30 minutes. This study demonstrated clinical efficacy in a number of domains, and achieved mean serum levels of 15.3mg/L, but also reported a significant risk of nausea and vomiting (15).

This highlights another dosing uncertainty, namely how long to infuse the medication over, as this will affect the pharmacokinetics of the drug. A recent systematic review of the loading dose found a poor relationship between dose administered and symptom resolution (16).

These uncertainties in dosing have not been addressed using physiologically based pharmacokinetic modelling (PBPK), where vast in-silico populations of children can be modelled to provide population estimates of PK. For IV aminophylline, this has only been undertaken for the current loading dose of 5mg/kg infused over 20 minutes, and it was found it would produce a serum concentration of <10mg/L in 70.3% of children, 10-20mg/ml in 29.4%, and >20mg/L in only 0.1% of children who receive it (17). This was corroborated by clinical data collected in the same study (17). However, almost all children would achieve a serum concentration of 5-15mg/L using this loading dose (Figure 1). Is the therapeutic range sub-optimal, the dose incorrect, or both? How does this compare with the one hour duration 10mg/kg loading dose?

Following the loading dose, an aminophylline infusion may be used to maintain the serum concentrations in the therapeutic range. There is even less data supporting the optimal dose (rate) of this infusion than there is for the loading dose. The recommended dose in the British National Formulary for Children (BNFC) for IV aminophylline infusion is based on age, with <11 years receiving 1mg/kg/hr and 12-18 years receiving 0.5-0.7mg/kg/hr (18), with both rates titrated to achieve the therapeutic range (10-20mg/L). The PK modelling work suggests that for younger children (0-11yrs) receiving 1mg/kg/hr initially, the mean steady state would be 16.4mg/L (95th centile range 5.3-32mg/L). Older children (12-18 years) on the 0.5mg/kg/hr infusion would achieve a mean concentration of 9.4mg/L (3.4-18mg/L), while the higher dose would achieve 13.3mg/L (4.7-25.0mg/L). There is clearly a wide range of possible outcomes related to the high inter-individual variation seen with this medication, and many children will be over- or under-dosed. The percentage of children who have very low serum concentrations (<5mg/L), sub-therapeutic (5-10mg/L), therapeutic (10-20mg/L) and supra-therapeutic (>20mg/L) are shown in *Table 1.*

## 3. Future research

That over 20 children died from acute asthma attacks in the UK in 2015 is unacceptable. While some of the deaths will have occurred before arrival at hospital, this should still serve as a stimulus to improve the treatment and outcomes for children with acute severe asthma in hospital. Several interconnected research strategies framed around the understanding of the disease, the classification of illness severity, the medications used, and the inter-individual variation present are required *(Figure 2).*

Before any drug studies are carried out, there is a need to determine and implement nationally the optimal method of collecting illness severity scores in childhood asthma. In the UK there is a 25 fold variation in emergency asthma admissions rates (19). Local Authorities in the North West of England include seven of the ten highest rates of emergency admissions for childhood asthma in the UK (20), however the mortality in this region is the same as the national average. Are the children admitted in areas like the North West more unwell? Do they have less access to preventative healthcare or greater environmental triggers? Or do the medical teams have lower thresholds for admission? Routine collection of validated paediatric asthma severity scores in paediatric ED departments would both help answer these questions, as well as streamlining the implementation of asthma clinical trials into hospitals nationally.

In parallel with this, observational PK studies linking aminophylline serum concentrations with clinically important outcomes need to be designed. This should be done in parallel with patients and parents, and use the core outcome set for paediatric asthma to guide the outcomes selected (21). For most dosing research, a new drug with unknown PK is tested at a range of doses, to look for alterations in biomarkers of the disease. However, we have an old drug, used in emergency situations at a standardised dose which is acceptable to UK clinicians, who are aware that in high concentrations significant adverse effects can occur. The evidence to date on IV aminophylline may not support the dose and therapeutic range as being optimal. It is therefore unlikely that in the extremely serious clinical scenario of an acutely unwell child with asthma who requires second line IV treatment, clinicians would accept randomisation to other doses that may decrease efficacy or increase adverse effects. It may therefore be necessary to undertake observational dosing research, using the existing clinical IV aminophylline dose.

The PBPK work has shown that there is considerable inter-individual variation in the concentrations achieved using the IV aminophylline dose commonly used in routine clinical practice. Prospective collection of data from children aligned with accurately timed Therapeutic Drug Monitoring sampling could provide a range of concentrations that could be linked to outcomes. If there are differences in the outcomes across the various serum concentrations achieved, then dose modification to maximise the proportion of children who achieve that concentration will need to be undertaken. The PBPK models already exist so this would be relatively quick to undertake and put into practice.

As well as establishing the PK-PD relationship for efficacy, we need to consider safety. The prospective collection of adverse effect data would need to be integral to an observational dosing study, and the optimal dose will likely be a balance between the efficacy and adverse effects. Even if the optimal benefit:risk ratio occurs at a serum concentration consistent with the current dosing, these data will provide assurance that current dosing strategies are appropriate.

Similarly, the serum concentrations targeted with the IV aminophylline infusion need to be examined. This will be additionally complicated by the titration of doses to meet the current therapeutic range. Careful consideration will be needed to decide whether to work within the current dosing methodologies and extract the most useful information to guide future treatments, or establish if clinical teams would be willing to undertake randomised trials in this area.

There may also be a place for stratified medicine in the dosing of aminophylline, particularly during the infusion, to guide rate. Theophylline is predominantly metabolised by CYP1A2 (22), which may have polymorphisms that affect clinical outcomes. The effects of the CYP1A2 polymorphisms on theophylline metabolism are poorly understood. Studies investigating this relationship are inconsistent, with some studies demonstrating an effect of the \*1F/\*1F polymorphism on expression and higher inducibility of CYP1A2 (23, 24). Including pharmacogenomic analysis with the collection of the PK data would therefore help answer this and other questions, and with the advent of bedside genetic testing for specific polymorphisms a path to implementation can be envisioned.

Even if an optimal dose of IV aminophylline is established, we are still not clear on which of the three IV treatments (aminophylline, salbutamol and magnesium sulphate) for acute severe asthma in children is optimal. There is a case for a randomised controlled trial (RCT) of the three IV treatments. One such study has already been undertaken, although there are concerns of excessive heterogeneity in the study group. The sample size was small (n=100), and the age range of the participants includes very young children down to age one, lower than UK paediatricians would reliably diagnose asthma. In addition the choice of beta-2 agonist (terbutaline) and the doses of magnesium and terbutaline used are not consistent with current UK practice (25).

The lack of evidence for aminophylline, as well as for the dose of salbutamol IV and expected effect sizes for all three IV treatment options means a definitive RCT in the UK is some way from reality (3, 26, 27). There is some progress, such as a recent PK study of salbutamol in PICU patients (28), but too many gaps in the evidence remain. Even if the evidence supporting the dose of aminophylline, salbutamol and magnesium sulphate were sufficient, this RCT would be a complex, expensive study, possibly prohibitively so, requiring multiple sites recruiting children in extremis, likely using a deferred consent model. Sites around the country will have their own standard of care, local guidelines that specify the order that the IV treatments are given, and therefore may not be in equipoise. Would cluster randomisation of centres be an acceptable way forward? How does the current variation in admissions for acute presentation affect the choice of sites and drugs used? What about clinicians who are not in equipoise? Clearly, expert clinical trials design and statistical input would be required to tackle these confounders.

It is possible to view this as too complicated, or too far from current implementation to consider, but for the children and young people affected, it is a question of vital importance. While any grand RCT remains out of reach, other initiatives are being picked up to help answer the important questions about IV aminophylline. We remain hopeful that as each question is answered, the goal of evidence based IV treatments for acute severe asthma moves closer.

## 4. Conclusion

The management of acute severe asthma includes IV aminophylline, but in common with the other IV treatments available, there is little supporting evidence for the current dosing regime. Prospective studies collecting pre-determined core outcomes, validated severity scores, PK parameters, adverse effects, and genomic data are needed to optimise the treatment of children with acute severe asthma using IV aminophylline.

## Compliance with Ethical Standards

The authors, Dr Gemma L. Saint, Dr Malcolm G Semple, Dr Ian Sinha and Dr Daniel B. Hawcutt have no conflicts of interest to declare. No funding was received to assist with the preparation of this manuscript.

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|  | **Children 0-12 years** | **Children 12-18 years** | |
|  | **Single dose infusion** | **Low dose infusion** | **High dose infusion** |
| **Steady state concentration of theophylline (mg/L)** | A loading dose of 5mg/kg aminophylline and 1mg/kg/h aminophylline infusion | A loading dose of 5mg/kg aminophylline and 0.5mg/kg/h aminophylline infusion | A loading dose of 5mg/kg aminophylline and 0.7mg/kg/h aminophylline infusion |
| **<5.0** | 4.5% | 15.9% | 5.5% |
| **5.0-<10.0** | 20.7% | 43.8% | 29.6% |
| **10.0-<20.0** | 48.0% | 37.4% | 50.2% |
| **≥20.0** | 26.8% | 2.9% | 14.7% |

**Table 1: The percentage of *in silico* paediatric patients (n=1000) receiving IV aminophylline (dosed appropriately for their age) who fall within defined steady state concentrations. Each in silico patient received an IV loading dose and IV infusion until steady state was reached. (Adapted from Cooney et al (13))**

# Figure Legends

Figure 1: Serum concentration time profile for theophylline in children age 1 month – 18 years modelled using PBPK software. Black line is mean profile, grey lines 5th and 95th percentiles and open circles clinical data. >95% achieve a serum concentration of 5-15mg/L (green lines) using the current 5mg/kg loading dose of aminophylline, however the current recommended therapeutic range is 10-20mg/L. (Adapted from Cooney et al (17))

Figure 2: Thematic areas in which research is required to improve the care of children with acute severe asthma

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