Salbutamol or aminophylline for acute severe asthma: how to choose which one, when and why?

Matthew Neame,¹ Octavio Aragon,² Ricardo M Fernandes,³,⁴ Ian Sinha¹

ABSTRACT
Acute, severe exacerbations of asthma present a challenge due to the significant morbidity associated with this presentation. For exacerbations that are refractory to initial treatments with inhaled and oral therapies, there is still doubt about which intravenous therapies are most likely to be helpful. β-2 agonists and aminophylline have differing mechanisms of action that also affect their adverse effects profiles and these are considered. A review of the available randomised control trials suggests that a bolus of intravenous salbutamol may reduce symptoms and hasten recovery. Aminophylline infusions may improve lung function, and in some studies have been shown to improve symptoms, but the evidence is not clear cut. 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.

INTRODUCTION
The pathophysiology of asthma exacerbations is complex. Exposure to a trigger induces a complex interplay of factors, including eosinophil and mast cell degranulation and epithelial damage. These cause histamine, prostaglandin and leukotriene release. Continuing T cell and B cell differentiation and proliferation, promoted by cytokine release, perpetuate this cascade. Subsequent inflammation, bronchoconstriction and mucus production cause airway obstruction and impairment of gas exchange.⁴

Although most children improve after inhaled bronchodilator by nebuliser or spacer, some require intravenous treatment. Magnesium sulfate is often used as the first-line intravenous therapy for such children.² In children who require additional intravenous therapy, salbutamol and aminophylline are used in practice, but there is no clear consensus around which should be used first.³ In this paper, we aim to summarise the pharmacological basis of these agents and evidence from randomised controlled trials (RCTs) relating to their efficacy and safety.

PHARMACOLOGY OF β-2 AGONISTS
Salbutamol and terbutaline are similar β-2 adrenoceptor agonists that are believed to exert their maximal therapeutic effect through bronchodilation. Stimulation of β-2 receptors in airway smooth muscle induces the cyclic AMP (c-AMP) pathway. c-AMP is a molecule with various cellular functions. Increased activity of c-AMP-dependent protein kinase A inhibits myosin phosphorylation and lowers intracellular calcium concentration, which in turn relaxes smooth muscle and causes bronchodilation.⁴ Increased intracellular c-AMP may also inhibit mast cell inflammatory mediator release (figure 1; adapted from refs. 5 and 6). Severe airway obstruction may restrict delivery of inhaled salbutamol to the airway epithelium, thus providing a theoretical rationale for the use of intravenous preparations. Because adrenoceptors are found in various organs and tissues, β-2 agonists can also cause various extrapulmonary adverse effects.

Pharmacokinetics
The half-life of salbutamol is 4–6 h, and it is excreted renally. The bronchodilatory effects of salbutamol are believed to occur at blood concentrations of between 5 and 20 ng/mL, and higher concentrations are thought to result in a greater risk of toxicity. There are limited data regarding the ideal dosing schedule for intravenous salbutamol in children.
A recent review commented on the relatively high doses per unit of weight advised for use in children compared with adult regimens and recommended further research into the pharmacodynamics and pharmacokinetics of intravenous salbutamol in the paediatric population.7

Cardiovascular effects
Salbutamol stimulates both β1 and β2 receptors in the heart and can reduce afterload through vasodilation and a drop in vascular resistance.8 9 These effects can cause significant tachycardia, postural hypotension and myocardial ischaemia.

Muscle tremors
Stimulation of β2 receptors in skeletal muscle may cause tremors, which can be uncomfortable for children.

Metabolic effects of β2 agonists
β2 agonists can cause hypokalaemia, in a dose-dependent fashion, because β2 receptors are linked to membrane bound Na+/K+ ATPase pumps. They can stimulate β2 receptors in both pancreatic islet cells and hepatocytes, causing increased insulin secretion (which can exacerbate hypokalaemia) and increased glycogenolysis, respectively.10 11 Patients treated with intravenous salbutamol may develop lactic acidosis because of β2-stimulated anaerobic glycolysis in muscle. This has been demonstrated in healthy subjects12 and has been observed in asthmatic individuals.13 14 There are reports of the subsequent metabolic acidosis contributing to a perception of increased respiratory distress with a concomitant and unnecessary treatment escalation or continuation. There do not seem to be reports of the lactic acidosis having any directly harmful consequences.

Tolerance
There is evidence that regular use of inhaled β2 agonists can modify the response of the β2 receptor resulting in reduced efficacy.15 This may make the use of intravenous salbutamol less beneficial in some cases, but the clinical significance of this finding in the management of acute exacerbations of asthma remains unclear.

PHARMACOLOGY OF AMINOPHYLLINE
Aminophylline is a methylated xanthine derivative. It is a combination of theophylline (the active component) and ethylenediamine, which is a compound that increases the solubility of theophylline but has no known intrinsic pharmacological effects.

The mechanisms of action of aminophylline are not completely understood. Beneficial effects may result from both bronchodilation and reduced airway hypersensitivity, but the extent to which each mechanism confers benefit at therapeutic doses is unclear.16 17 Effective use of the drug also requires a consideration of its pharmacokinetics.

Pharmacokinetics
Aminophylline has a narrow therapeutic range, and the associations between elevated levels and unwanted effects are important to consider. The bronchodilator
<table>
<thead>
<tr>
<th>Administration details</th>
<th>Reconstitution details</th>
<th>Calculation complexity</th>
<th>Therapeutic risk risk</th>
<th>Need to use part vials</th>
<th>Different strengths available</th>
<th>Need for infusion pump</th>
<th>Other</th>
<th>Fluid compatibility</th>
<th>Additive</th>
<th>Y-site</th>
<th>Monitoring</th>
<th>U&amp;Es</th>
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</tr>
<tr>
<td>Aminophylline</td>
<td>No, solution</td>
<td>Yes: multistep calculation for dilution and rate</td>
<td>High: narrow therapeutic index drug</td>
<td>Yes: for loading dose</td>
<td>Yes/no: for maintenance infusion depending on house recommendations</td>
<td>No</td>
<td>Yes</td>
<td>Sodium chloride 0.9% and 0.45%</td>
<td>Dextrose 5%</td>
<td>Combination of the above</td>
<td>As above</td>
<td>Yes</td>
</tr>
<tr>
<td>Salbutamol infusion</td>
<td>No, solution</td>
<td>Yes: multistep calculation for dilution and rate</td>
<td>High</td>
<td>Yes</td>
<td>Also for larger patients need to use multiple vials to avoid multiple bag changes</td>
<td>Yes</td>
<td>Yes</td>
<td>Sodium chloride 0.9% and 0.45%</td>
<td>Dextrose 5%</td>
<td>Combination of the above</td>
<td>As above</td>
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</tr>
<tr>
<td>Salbutamol bolus</td>
<td>No, solution</td>
<td>Yes: multistep calculation for dilution and rate</td>
<td>High</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Sodium chloride 0.9% and 0.45%</td>
<td>Dextrose 5%</td>
<td>Combination of the above</td>
<td>As above</td>
<td>No</td>
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<table>
<thead>
<tr>
<th><strong>Table 1 Continued</strong></th>
<th><strong>Aminophylline</strong></th>
<th><strong>Salbutamol infusion</strong></th>
<th><strong>Salbutamol bolus</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECG</strong></td>
<td>▶ Yes: during loading dose</td>
<td>▶ Yes</td>
<td>▶ Yes</td>
</tr>
<tr>
<td></td>
<td>▶ Often continues during maintenance infusion</td>
<td>▶ HDU bed recommended</td>
<td>▶ May be given in A&amp;E</td>
</tr>
<tr>
<td></td>
<td>▶ HDU bed recommended if available (administration should not be delayed if unavailable)</td>
<td>▶ BP and heart rate</td>
<td>▶ BP and heart rate</td>
</tr>
<tr>
<td></td>
<td>▶ BP and heart rate</td>
<td>▶ Vast range of doses: 0.1–10 μg/kg/min. (Although note that when prescribing for children the maximum adult dose suggested in the BNF of 20 μg/min will often be surpassed. A total dose cap should be considered for larger children)</td>
<td>▶ Set dose (may be repeated if needed)</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>▶ Variates with age</td>
<td>▶ Use ideal body weight</td>
<td>▶ Cap dose at 250 μg</td>
</tr>
<tr>
<td></td>
<td>▶ Use ideal body weight</td>
<td>▶ Calculate and prescribe different doses for loading dose and maintenance infusion: use standard concentration recommended</td>
<td>▶ Over 5–20 min</td>
</tr>
<tr>
<td></td>
<td>▶ Calculate and prescribe different doses for loading dose and maintenance infusion: use standard concentration recommended</td>
<td>▶ 2 prescriptions, one for loading dose, one for maintenance infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ No blind loading dose recommended for patient on theophylline therapies at home or with renal/liver impairment</td>
<td>▶ No blind loading dose recommended for patient on theophylline therapies at home or with renal/liver impairment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Cap loading dose at 500 mg</td>
<td>▶ Vast range of doses: 0.1–10 μg/kg/min. (Although note that when prescribing for children the maximum adult dose suggested in the BNF of 20 μg/min will often be surpassed. A total dose cap should be considered for larger children)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Adjust rates depending on levels and side effects</td>
<td>▶ Conversion mg-micrograms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Low metabolic interaction risk</td>
<td>▶ Conversion hours-minutes</td>
<td></td>
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<tr>
<td></td>
<td>▶ High metabolic interaction risk</td>
<td>▶ Difficult to use a standard concentration due to variability in doses</td>
<td></td>
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<tr>
<td></td>
<td>– Aciclovir,azole antifungals, macrolides, quinolones,calcium channel blockers, etc., will raise theophylline concentrations</td>
<td>▶ Adjust rates depending on clinical picture and side effects</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Some antiepileptics, rifampicin, tobacco smoke will reduce theophylline concentrations</td>
<td>▶ Low metabolic interaction risk</td>
<td></td>
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<tr>
<td></td>
<td>▶ Additive hypokalaemia with common concomitant treatments (steroids, salbutamol)</td>
<td>▶ Antidiabetic agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>▶ Pharmacokinetics vary greatly with age:</td>
<td>▶ Additive hypokalaemia with common concomitant treatments (steroids, aminophylline)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Neonates and infants under 6 months slower clearance than adults</td>
<td>▶ Low metabolic interaction risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Infants and children up to 9–10 faster clearance than adults</td>
<td>▶ Antidiabetic agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– Gender different clearance in adolescents</td>
<td>▶ Additive hypokalaemia with common concomitant treatments (steroids, salbutamol)</td>
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<tr>
<td></td>
<td>▶ Requires pharmacy input for dosage adjustments, how long to stop, how much to re-load with etc.</td>
<td></td>
<td></td>
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<tr>
<td><strong>Drug particulars</strong></td>
<td></td>
<td>▶ Requires pharmacy input for dosage adjustments, how long to stop, how much to re-load with etc.</td>
<td></td>
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<tr>
<td>▶ Low metabolic interaction risk</td>
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<tr>
<td>▶ Antidiabetic agents</td>
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<td>▶ Additive hypokalaemia with common concomitant treatments (steroids, aminophylline)</td>
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<tr>
<td>▶ Additive hypokalaemia with common concomitant treatments (steroids, aminophylline)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prescription ease</strong></td>
<td>▶ Licensed in children older than 6 months</td>
<td>▶ Licensed for children older than 12 years</td>
<td>▶ Licensed for children older than 12 years</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td></td>
<td>▶ Licensed for children older than 12 years</td>
<td></td>
</tr>
</tbody>
</table>

A&E, accident and emergency; BNF, British National Formulary; HDU, high-dependency unit; U&E, urea and electrolytes.
effects of theophylline are proportional to the log of its concentration—in other words, increasing theophylline plasma concentration causes a less than proportional increase in bronchodilation, such that levels higher than 20 mg/L are unlikely to offer additional therapeutic benefit but will increase the risk of toxicity. Furthermore, clearance rates are affected by factors including age and the use of cytochrome P450 inducers and inhibitors. This makes careful dosing and regular assessments of serum theophylline levels crucial.

Mechanism of bronchodilation
Aminophylline may cause bronchodilation through effects on c-AMP by inhibiting certain phosphodiesterase enzymes (figure 1). Phosphodiesterases degrade intracellular c-AMP molecules, so their inhibition may result in increased levels of intracellular c-AMP and subsequent airway smooth muscle relaxation.\textsuperscript{18} Interestingly, however, the degree of phosphodiesterase inhibition is not particularly significant at therapeutically relevant theophylline concentrations.\textsuperscript{19} Furthermore, other drugs that inhibit phosphodiesterases more significantly are not thought to have significant bronchodilator effects at therapeutic doses (ie, roflumilast, cilomilast). Other hypotheses around the bronchodilator effects of aminophylline are that it can act by blocking adenosine receptors (adenosine has little effect on human airway muscle in vitro but can cause bronchoconstriction in asthmatic subjects when given by inhalation) and that it induces catecholamine release with subsequent adrenergic stimulation.\textsuperscript{20} It is possible, therefore, that aminophylline acts on more pathways than salbutamol.

Immunomodulation
Other benefits in asthma exacerbations may relate to immunomodulation and anti-inflammatory effects. Long-term use of oral theophylline can reduce the numbers and activity of eosinophils in bronchial mucosa.\textsuperscript{21} Aminophylline might also exert anti-inflammatory effects by enhancing neutrophil apoptosis via adenosine receptor antagonism\textsuperscript{22} or by inhibiting histones required for activation of inflammatory gene transcription.\textsuperscript{23} These effects can occur at low or subtherapeutic plasma theophylline concentrations.

Seizures
In case series, aminophylline has been implicated in the development of seizures in children, some of whom have not had underlying epilepsy, and in some cases theophylline levels remained within the recommended therapeutic range.\textsuperscript{24–26} Although the mechanism for this is unknown, it has been proposed that aminophylline may modulate the brain’s usual seizure threshold through blocking adenosine receptors.\textsuperscript{27}

Cardiac effects
Tachycardia is a common dose-dependent side effect of aminophylline and oral theophylline.\textsuperscript{25} In adults, theophylline has been implicated in the development of serious atrial tachyarrhythmias. It is not clear to what extent this risk extends to the paediatric population.

Vomiting
Vomiting is a common adverse effect of aminophylline and theophylline. It can happen at any plasma concentration, but is more common at supratherapeutic levels.\textsuperscript{25}

RCTS OF SALBUTAMOL (OR TERBUTALINE) AND AMINOPHYLLINE
We identified RCTs that assessed the use of intravenous salbutamol, terbutaline or aminophylline in the paediatric population after searching the Cochrane register of controlled trials. The identified trials have been summarised in a series of tables (see online supplementary tables S1–S3), and the main findings are outlined in the text below.

In three RCTs, intravenous salbutamol or terbutaline therapy have been compared with either placebo or nebulised treatment in a total of 130 children with acute asthma. Two of these\textsuperscript{W1 W2} were conducted in the emergency department (ED) and assessed the efficacy of a bolus of salbutamol, and one\textsuperscript{W3} assessed the efficacy of a terbutaline infusion in a paediatric intensive care unit (PICU) setting.

Only one trial\textsuperscript{W1} reported benefit with regards to the assessment of clinical severity. One trial showed no difference, and in one trial the outcome was not reported. No trials reported lung function outcomes. Neither of the trials conducted in ED reported the rates of admission to PICU. Length of hospital stay was improved in the group receiving intravenous salbutamol in one trial conducted in ED,\textsuperscript{W2} but was not reported in the other.\textsuperscript{W1} Two of these studies were included in a Cochrane review,\textsuperscript{28} which concluded that there was very little evidence to support the addition of intravenous salbutamol to nebulised therapy in children with acute asthma exacerbations.

Aminophylline has been compared with placebo or usual treatment (one study compared a control group who were managed with continuous nebulised albuterol, inhaled ipratropium and intravenous methylprednisolone with an aminophylline group given the above plus intravenous aminophylline) in children with acute asthma exacerbations in 12 RCTs involving 586 children.\textsuperscript{W4–15} Three were conducted in ED, seven on hospital wards, one on PICU and in one study reported as a conference abstract the setting was unclear.

Three trials found that aminophylline improved clinical severity scores, but six did not. Three trials did not report this outcome. Two trials showed improved lung function scores, two did not and eight did not report this outcome. One trial showed that aminophylline reduced PICU admission rates, but...
none of the other studies reported any results for this outcome. No trials have found any benefit of amino-
phylline on length of hospital or PICU stay (seven found no difference, and five did not report this
outcome). Also, 7 of these 12 trials have been included in a Cochrane review.29 The review con-
cluded that intravenous aminophylline improved lung function within 6 h of treatment, but did not appear
to reduce symptoms or length of hospital stay, and there was insufficient evidence to evaluate its impact
on PICU rates.

Intravenous aminophylline and salbutamol (or ter-
butaline) have been compared, head-to-head, in four
RCTs involving 202 children.W16–19 Two were con-
ducted in hospital wards, and one in PICU. In one
RCT, reported as a conference abstract, the setting
was unclear.

In the three trials that reported results for clinical
severity scores, there was no difference between salbu-
tamol and aminophylline. No studies reported lung
function outcomes. In the one study reporting PICU
admission rates, there was no difference between ami-
ophylline and salbutamol. In two studies reporting
length of hospital stay, there was no difference
between groups, and in two studies this outcome was
not reported. These paediatric studies have been
included in a subgroup analysis in a Cochrane
review.30 The review concluded that there was no con-
sistent evidence to help decide between aminophylline
and salbutamol as the first-line intravenous therapy of
choice.

It is difficult to draw clear conclusions from RCTs
about the relative safety profiles of the two treat-
ments. There is wide variability in the assessment and
reporting of adverse effects associated with the two
treatments in clinical trials. It would appear that sal-
butamol does carry a risk of cardiovascular adverse
effects. In one study, W3 6/25 children treated with ter-
butaline had raised troponin-I levels and one was
withdrawn because of arrhythmia. In one trial com-
paring salbutamol with aminophylline, the group
receiving salbutamol demonstrated a significant trend
towards tachycardia. Nausea and vomiting were the
most commonly reported adverse effects associated
with the use of intravenous aminophylline, as dem-
onstrated in several trials and in a Cochrane review.29 In
the trials involving intravenous aminophylline assessed
for this review, there was only one reported case of a
seizure.

SUMMARY
Salbutamol and aminophylline cause bronchodilation
in airways of children with exacerbations of asthma.
Both agents probably work by inducing the c-AMP
pathway, which reduces intracellular calcium concen-
trations, thereby relaxing airway smooth muscle.

Multiple choice questions

1. Which process is not a factor in the pathophysiology
   of an acute exacerbation of asthma?
   A. bronchoconstriction
   B. vasoconstriction
   C. mucus formation
   D. inflammation
   E. mast cell degranulation.

2. Which effect has not been suggested as a potential
   mechanism of action for aminophylline?
   A. bronchodilation through inhibition of airway
      smooth muscle cell phosphodiesterases and sub-
      sequent increases in intracellular c-AMP
      concentrations;
   B. bronchodilation via blockade of pulmonary adeno-
      sine receptors;
   C. reduction of eosinophil activity in bronchial
      mucosa;
   D. reduction of mucosal secretions through inhibition
      of epithelial sodium transporter channels;
   E. inhibition of histones required for activation of
      inflammatory gene transcription.

3. Which adverse effect is not associated with the use
   of intravenous salbutamol?
   A. lactic acidosis
   B. hypokalaemia
   C. tremor
   D. myocardial ischaemia
   E. hyponatraemia.

4. Which adverse effect is not associated with the use
   of intravenous aminophylline?
   A. seizures
   B. nausea
   C. hypertrichosis
   D. tachycardia
   E. headache.

5. Which statement is true?
   A. Aminophylline has a narrow therapeutic index,
      but reliable serum levels can always be achieved
      by following recommended dosing guidelines.
   B. If adverse effects occur with the use of intraven-
      ous aminophylline, the serum levels will be above
      the recommended limits.
   C. If serum theophylline levels are below the advised
      limits, the rate of the infusion should be increased
      immediately.
   D. If a patient takes oral theophylline, they should
      not receive a loading dose of intravenous
      aminophylline.
   E. The ethylenediamine compounds attached to
      theophylline in order to make aminophylline are
      thought to contribute to its bronchodilatory
      effects.

Answers are on page 222.
Aminophylline may have additional mechanisms of action, which are poorly understood. Both agents also have extrapulmonary adverse effects, which can be dangerous or distressing to children.

The evidence from RCTs for the intravenous administration of either drug to children during an asthma exacerbation is minimal and inconsistent. A bolus of intravenous salbutamol may reduce symptoms and hasten recovery.21 Aminophylline infusions may improve lung function, and in some studies have been shown to improve symptoms, but this finding is not replicated in all studies. It is unlikely that either agent reduces PICU admission rates or length of hospital stay, but these evaluations are hampered because many studies do not report these outcomes. Adverse effects were noted with the use of both treatments, but the available evidence does not enable comparison of the likelihood of adverse effects with either treatment.

Despite the minimal evidence of benefits from RCTs, intravenous therapy probably does have a role in managing certain children with either refractory or severe exacerbations of asthma, and those who have previously required PICU admission. Variation of practice at individual clinician and departmental level is likely to continue with regards which of these agents should be used first. Given that intravenous agents are likely to remain in widespread use, we suggest that the choice should take into account factors such as ease of prescription, preparation and administration (which have direct implications for risk management), availability of high-dependency beds and nursing preference. These factors are summarised in table 1.

Whichever therapy is used, we would advocate that children are assessed for objective markers of improvement of clinical status after the initial loading dose bolus to evaluate whether they really need to be treated with a subsequent infusion or not. We would also stress the importance of stringent, routine monitoring of the adverse effects that we have highlighted. Current uncertainty about these therapies, including guidelines on how drug levels and adverse effects should be monitored in children, must be addressed in future research studies.

Contributors The original idea for this article came from IS, who suggested a review of the evidence around the use of intravenous salbutamol and aminophylline focusing on their mechanisms of action, efficacy and safety. The literature search and suggestions for subheadings within the pharmacology sections came from MN, OA and RF. The literature search for randomised control trials was conducted by IS and MN. The tables in the online supplementary file were produced by MN. The first draft of the article was produced by MN and was edited by IS after discussion between all the authors. IS is the guarantor for the paper.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

REFERENCES


Answers to the multiple choice questions

1. B
2. D
3. E
4. C
5. D