Intravenous salbutamol for childhood asthma: evidence-based medicine?

E S Starkey, H Mulla, H M Sammons, H C Pandya

ABSTRACT
Intravenous salbutamol is commonly used to treat children with severe asthma unresponsive to inhaled β2-agonist therapy. However, in this setting, there is little clinical trial data demonstrating its effectiveness. Additionally, there are significant concerns that intravenous salbutamol-dosing recommendations for children with acute asthma are excessive, and unnecessarily raise the potential for adverse reactions, such as lactic acidosis and tachycardia which, by increasing respiratory workload, exacerbate respiratory failure. Here, we review salbutamol clinical pharmacology and toxicology, evidence relating to its use in acute asthma and highlight important gaps in the evidence base.

INTRODUCTION
Asthma exacerbations are a common occurrence in children. At presentation, management begins with a rapid physical examination to assess severity and guide initial therapy. Most children respond to frequent inhaled salbutamol (albuterol), oxygen as needed, and systemic corticosteroid therapy. Despite a paucity of data, intravenous salbutamol is recommended by some guidelines as first-line adjunctive therapy. Here, we review salbutamol pharmacology, the evidence relating to use of intravenous drug in acute asthma and highlight important gaps in the evidence.

SALBUTAMOL—ROUTE OF ACTION
Salbutamol is a selective β2-adrenoreceptor agonist which ‘relaxes’ airway wall smooth muscle (ASM) irrespective of the mechanism leading to contraction. Hence, its bronchodilator action is dependent on achieving an effective concentration in walls of conducting airways. As it is not possible to determine the ‘ASM-tissue concentration/ASM-response’ relationship for salbutamol, the ‘blood-concentration/ASM-response’ relationship is commonly used as a surrogate measure.

When inhaled, salbutamol is absorbed into the pulmonary circulation via the alveolar epithelium. There is also evidence to suggest that epithelial cells of conducting airways transport drug from luminal to basal surfaces, that is, into the walls of conducting airways. This suggests that inhaled drug delivery should achieve higher ASM tissue salbutamol concentrations than the intravenous route, on a dose-for-dose basis. However, delivery of inhaled drug to airways may be attenuated by poor technique and/or severe airflow obstruction. This provides a rationale for intravenous therapy. Salbutamol toxicity is mediated by stimulation of β1 and β2 adrenoreceptors located outside the lungs. Consequently, salbutamol dose-toxicity relationships are governed by its concentration in blood.

Irrespective of the means by which salbutamol is delivered to airways, there is no evidence to suggest that relaxation responses of ASM cells in developing airways are significantly different to ASM cells in adult airways. Studies of airway development show that ASM cells are part of the airway wall from the earliest stages of lung development, and that ASM cells in prenatal and postnatal airways have the same contractile machinery. Furthermore, ASM from fetal human lungs is myogenic and responds to contractile agonists and relaxants. Nonetheless, wheeze and respiratory distress are not always responsive to salbutamol therapy, particularly in infancy. Acute airflow obstruction due to airway wall oedema and/or mucus plugging, as might occur in acute bronchiolitis, is not relieved by salbutamol. There is no convincing data to show that infants with recurrent/persistent wheeze benefit from salbutamol either. Physiological measures of airflow obstruction show that salbutamol does reduce airflow obstruction in some with recurrent/persistent wheeze. However, most have no response to salbutamol or respond paradoxically. These findings support the presence of functional β2 adrenoreceptors and ASM in the very young. The lack of clinical benefit implies that airflow obstruction in this group of patients is not predominantly due to ASM-induced bronchoconstriction.

SALBUTAMOL PHARMACOKINETICS, PHARMACODYNAMICS AND TOXICITY
The pharmacodynamics (PD) and pharmacokinetics (PK) of salbutamol in children and adults appear to be similar. Once in the systemic circulation, salbutamol is cleared directly by renal excretion or metabolised to the inactive 4'-sulphate which is then excreted in urine. The half-life of salbutamol in plasma is 4–6 h. Hence, relatively frequent dosing with inhaled drug, a loading dose followed by a continuous infusion of intravenous drug or some combination of inhaled and intravenous therapy is required to maintain therapeutic concentrations of drug in blood.

Inhaled and intravenous salbutamol dosing should be based on estimates of volume of distribution (V) and clearance (CI) generated through PK studies. The very limited amount of PK data relating to salbutamol indicate that while estimates of V and CI following inhaled salbutamol are

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significantly different to those obtained after intravenous administration of drug.\textsuperscript{12–17} Age does not significantly affect estimates of V and Cl for either the inhaled or the intravenous route of drug administration. Although this latter observation somewhat contrasts with the principle that drug Cl increases non-linearly with age,\textsuperscript{18} the available PK data indicates that intravenous salbutamol dosing for children and adults should still relate reasonably closely.

The bronchodilator action of salbutamol in stable asthma is associated with blood concentrations between 5 and 20 ng/mL for children and adults.\textsuperscript{12,13,19–21} Multiple doses of inhaled salbutamol, as might be used in an acute attack of asthma, generate blood concentrations between 20 and 40 ng/mL.\textsuperscript{19–23} The blood concentration of salbutamol associated with adverse reactions in children is not known. In adults, salbutamol toxicity is associated with blood concentrations greater than 30 ng/mL with a putative lethal level of >160 ng/mL.\textsuperscript{25} Very high blood salbutamol concentrations (196–586 ng/mL) have been recorded in children receiving intravenous salbutamol and mechanical ventilation for severe asthma.\textsuperscript{23,24} The intravenous salbutamol doses given to children in these case reports were in keeping with those recommended in current intravenous salbutamol dosing guidance.

Common adverse reactions associated with salbutamol therapy in children include tremor, hypokalaemia, increased lactate, hyperglycaemia and sinus tachycardia.\textsuperscript{1} Treatment-related supraventricular tachycardia is uncommon;\textsuperscript{1,5} 23 Blood salbutamol concentrations in children and adults dying during the course of an asthma attack have been found to range from 1 to 787 ng/mL.\textsuperscript{28} Compared to a control group of individuals who recovered from an asthma exacerbation, individuals who died had significantly higher mean blood salbutamol concentrations (geometric mean=11.5 ng/mL and 33.5 ng/mL, respectively). Those with the highest blood salbutamol concentrations were given nebulised and intravenous drug concurrently. The known toxic effects of salbutamol have significant implications for patients and clinicians; β-adrnergic receptor stimulation heightens patient anxiety; lactic acidosis and tachycardia increase respiratory workload, and so exacerbate respiratory failure. Hence, while it should always be possible to detect a worsening clinical picture in a child with severe asthma on high-dose salbutamol therapy, it may not always be easy to determine whether deterioration is due to worsening asthma, salbutamol toxicity or a combination of the two. Moreover, taking appropriate measures in these circumstances requires significant clinical experience and a thorough understanding of salbutamol clinical pharmacology.

**Intravenous Salbutamol Dosing Recommendations for Children**

Intravenous salbutamol is only licensed for adults and children over 12 years. The license does not extend to children under 12 years of age due to a lack of safety and effectiveness data (see table 1).\textsuperscript{4,5}

Table 1 Intravenous salbutamol dosing recommendations in British National Formularies for Children (BNFc) and adults (BNF)

<table>
<thead>
<tr>
<th>Adults (BNF)</th>
<th>Children BNFc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bolus dose</strong></td>
<td><strong>Continuous infusion</strong></td>
</tr>
<tr>
<td>250 mcg slow intravenous injection</td>
<td>3–20 mcg/min</td>
</tr>
<tr>
<td>Less than 2 years age=5 mcg/kg</td>
<td>1–5 mcg/kg/min</td>
</tr>
<tr>
<td>Over 2 years age=15 mcg/kg; maximum 250 mcg</td>
<td></td>
</tr>
<tr>
<td>All doses over 5 min</td>
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</tbody>
</table>

All childhood asthma treatment guidelines recognise that dosing recommendations for intravenous salbutamol are not founded on age-appropriate PK-PD data.\textsuperscript{1–5} Possibly as a result, these guidelines are inconsistent with respect to salbutamol dosing in children. By way of example, for those over 2 years of age, UK British Thoracic Society/Scottish Intercollegiate Guideline Network (BTS/SIGN) asthama guideline recommends 15 mcg/kg (to a maximum of 250 mcg) intravenous bolus dose over 10 min and a continuous infusion of 1–5 mcg/kg/min. However, there is no guidance for children less than 2 years of age.\textsuperscript{1} By contrast, the UK paediatric formulary (BNFc) recommends the same bolus dose for over 2 years of age, but 5 mcg/kg bolus dose for children under 2 years of age with all bolus doses given over 5 min rather than 10 min as per BTS/SIGN guidance.\textsuperscript{4} While these differences appear trivial at first glance, it is worth remembering that a bolus dose given over 5 min potentially generates higher blood concentration, and hence increases the risk of adverse effects, than one given over 10 min. To confuse matters further, there are no recommendations about concomitant use of nebulised β2-agonists during intravenous therapy.

**Intravenous Salbutamol Dosing Recommendations for Adults**

Unlike children, the dosing schedule for intravenous salbutamol in adults is founded on PK-PD data and defined in the Summary of Product Characteristics (SmPC).\textsuperscript{4,5} The intravenous bolus dose recommended for adults is 250 μg over 5–10 min; the continuous infusion rate is 3–20 μg/min.\textsuperscript{4} Based on the average adult weighing 70 kg, the bolus and continuous infusion doses for adults approximately equate to 3.5 μg/kg over 5–10 min and 0.04–0.29 μg/kg/min, respectively.

Clearly, intravenous salbutamol doses for children are an order of magnitude higher than those recommended for adults. The huge differences in doses for adults and children are inconsistent with the predicted similarity in their salbutamol PK-PD relationship. More importantly, higher doses could translate to an increased risk of toxic reactions, and the inconsistencies in dosing regimens are liable to engender uncertainty and confusion among clinicians.\textsuperscript{23,26} For example, using dosing regimens recommended by the BNFc, a child weighing 20 kg and over 2 years of age will receive the same intravenous bolus dose as that recommended for a 70 kg adult.\textsuperscript{4,5} At the lowest continuous infusion rate (1 μg/kg/min) recommended by the BNFc, the same child would then receive 300 μg every 15 min. By contrast, an adult would only receive the same dose of salbutamol intravenously in 15 min at the highest continuous infusion rate (20 μg/min or ~0.29 μg/kg/min) recommended for this population.

**Evidence Base for Intravenous Salbutamol Dosing Regimens in Children**

The few studies on the use of intravenous salbutamol in the paediatric population have tested an intravenous bolus dose of 1.5 μg/kg (with no limit on total dose) administered over 10 or 20 min.\textsuperscript{26–31} Two of the studies based their dosing regimen on an earlier study in which children receiving regular inhaled salbutamol received either a bolus of intravenous salbutamol or intravenous placebo (N=14)\textsuperscript{29} soon after presentation. In this study, Browne et al reported that children given intravenous drug recovered faster and spent less time in hospital.\textsuperscript{29} However, all patients received only one salbutamol nebuliser...
prior to administration of intravenous drug or placebo which is very different to present day practice.

Browne et al state they based their bolus dose on a ‘linear extrapolation’ of doses used by Goldstein et al in a phase 1 study of otherwise healthy adults. In this latter study, 10 volunteers (average weight of 72 kg) received 1.5 mg of intravenous salbutamol over 30 min which equates to 7 μg/kg over 10 min. Hence, the 15 μg/kg dose of intravenous salbutamol used in the study by Browne et al does not appear to be a linear extrapolation of doses used by Goldstein et al. Furthermore, as Goldstein et al is primarily a PK study involving otherwise healthy adults, it should be used as the starting point for developing intravenous salbutamol dosing schedules for children. Any intravenous salbutamol dosing regimen should also take prior inhaled drug doses into account and data from dose-response and tolerability studies which for adults, prior to Goldstein et al, reported that bronchodilator responses plateau at intravenous bolus doses of between 200 and 300 μg. Additionally, these studies reported that autonomic adverse effects become increasingly more common with bolus doses over 200 μg, and that intravenous doses of greater than 500 μg (~7 μg/kg) are often poorly tolerated due to profound cardiovascular adverse effects.

The evidence base for the current salbutamol continuous infusion regimen in children is also very poor. It largely consists of case reports from over 30 years ago relating to children with severe asthma requiring mechanical ventilation. The effectiveness and tolerability of continuous infusion salbutamol has been investigated more rigorously in adults using doses ranging from 4 to 80 μg/min. Together, these studies show that bronchodilator responses peak at a continuous infusion rate between 5 and 20 μg/min. Higher continuous infusion doses only result in increased cardiovascular adverse effects. Thus, the available PK-PD data suggests that the maximal licensed continuous infusion dose for salbutamol (20 μg/min) in adults is reasonable, as adverse effects outweigh any potential benefits using higher rates. Adjusted for weight, the maximal recommended continuous infusion rate for salbutamol in adults is around 0.29 μg/kg/min which is significantly lower than the 1–5 μg/kg/min currently recommended continuous infusion doses for children less than 12 years of age.

In the absence of robust clinical data, drug modelling methods can provide information regarding kinetics of intravenous salbutamol. Figure 1 shows simulated plasma salbutamol kinetics in drug-naive 3, 7 and 12-year-olds, and a 70 kg adult. The simulated mean plasma salbutamol concentration profiles for children treated with intravenous salbutamol doses recommended in the BNF achieve are much higher than adults (treated according to SmPC guidance). Table 2 is a summary of maximum plasma concentration (Cmax) and area under the curve (AUC) values for intravenous salbutamol kinetics shown in figure 1. Since AUC (total systemic exposure to drug) and Cmax correlate with drug effectiveness and safety, this simulated data further highlight recognised concerns regarding use of intravenous salbutamol. In developing these profiles, the continuous infusion doses chosen were the lowest recommended for children and adults, and that values for V and CI for children were allometrically interpolated from adult values. Also, in clinical practice, children are likely to have had several inhaled doses of salbutamol prior to commencing intravenous drug therapy.

### INTRAVENOUS SALBUTAMOL AND OUTCOMES

Assessing the effectiveness of intravenous salbutamol depends on outcomes used to measure success. Although peak flow is one marker of bronchodilator effectiveness, most patients and clinicians would consider relief of respiratory distress, time spent in oxygen, HDU and overall hospital stay, as important in relation to intravenous salbutamol therapy. However, there is scant paediatric data on whether intravenous salbutamol alters any of these important measures of outcome.

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**Table 2** Predicted systemic exposure to salbutamol following intravenous administration in children and adults

<table>
<thead>
<tr>
<th></th>
<th>Bolus only 15 mcg/kg (max 250 mcg)</th>
<th>Bolus + CI Bolus=15 mcg/kg (max 250 mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cmax (ng/mL)</td>
<td>AUC (hr.ng/mL)</td>
</tr>
<tr>
<td>Adult (70 kg)</td>
<td>7.2</td>
<td>8.9</td>
</tr>
<tr>
<td>Child 3 years (14 kg)</td>
<td>28.9</td>
<td>24.9</td>
</tr>
<tr>
<td>Child 7 years (23 kg)</td>
<td>21.3</td>
<td>20.2</td>
</tr>
<tr>
<td>Child 12 years (39 kg)</td>
<td>12.8</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Simulations for children were developed on 15 mcg/kg (max 250 mcg) bolus dose over 10 min followed by continuous infusion (CI)=1 mcg/kg/min for 3 h. Simulations for adults were developed on a 250 mcg bolus dose over 10 min and CI=3 mcg/min for 3 h. AUC, area under curve (total systemic exposure); Cmax, maximum plasma concentration.
One Cochrane systematic review on intravenous β2-agonists in asthma (15 studies N=584, all age groups) concluded that neither intravenous salbutamol nor intravenous terbutaline were any more effective in improving peak expiratory flow rate than inhaled salbutamol. This review found few studies reporting outcomes in children, particularly in the paediatric environment. Another review of adding intravenous β2-agonists (salbutamol) to inhaled therapy included three studies, of which two were limited to children (N=56 patients). This too was unable to draw firm conclusions other than that more research was needed to assess the effectiveness and safety of intravenous salbutamol.

**GENERATING AN EVIDENCE BASE FOR INTRANEOUS SALBUTAMOL IN CHILDREN**

Although intravenous salbutamol is widely used to treat children with a severe exacerbation of asthma, the current evidence base is poor and recognised to create uncertainty. The substantially higher doses recommended for children pose a potential toxicity risk with no proven additional clinical benefit. Thus, as recommended by current guidelines, children on intravenous salbutamol therapy should be carefully monitored in high-dependency or intensive-care environment.

A better understanding of intravenous salbutamol is needed to allow robust evaluation of its usefulness in children with severe acute asthma. There are several questions which stem from the present review. These include (1) is intravenous salbutamol therapy efficacious and safe in the treatment of acute severe asthma? (2) what is the optimal intravenous bolus and CI doses for salbutamol across the age range 0–16 years? (3) should inhaled β2-agonist therapy be stopped during intravenous salbutamol therapy? and (4) what are the risks of using intravenous salbutamol at high doses, and are there any biomarkers that could indicate toxicity?

While there are no easy and quick ways of answering these questions, in our view, a ‘bottom-up’ approach seems the most safe and efficient. In practical terms, this means defining the PK-PD for intravenous salbutamol in childhood acute asthma before conducting ‘head-to-head’ comparative effectiveness and safety trials. It is clear that a better understanding of intravenous salbutamol will benefit children with asthma.

**Competing interests** None.

**Provenance and peer review** Commissioned; externally peer reviewed.

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