Special review

Intravenous Salbutamol: Too Much of a Good Thing?

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ABSTRACT

Objective: To review the evidence for the use of intravenous salbutamol, its systemic effects and the potential complications that may occur in patients with severe asthma.

Data sources: A review of articles reported on intravenous salbutamol in patients with acute asthma.

Summary of review: Intravenous salbutamol is recommended in the treatment of severe asthma when there is failure to respond to nebulised β₂-agonists. To date, however, there are no published trials that establish the efficacy or safety of the combination of inhaled salbutamol and a continuous intravenous salbutamol infusion over inhaled salbutamol alone for treatment of severe acute asthma. β₂-agonists have numerous systemic actions that may adversely affect patients with severe respiratory compromise. The most important of these is the potential for β₂-agonists to cause a lactic acidosis, which, by increasing respiratory demands, could precipitate respiratory failure.

Conclusions: Systemic salbutamol has metabolic effects that may worsen respiratory function in asthma and should not be given by intravenous infusion to asthma patients outside of clinical trials. For patients who fail to respond to inhaled β₂-agonists, ipratropium and systemic steroids, consideration should be given to other therapies such as non-invasive ventilation rather than increasing the dose of a drug that may paradoxically worsen respiratory function (Critical Care and Resuscitation 2005; 7: 119-127)

Key words: Salbutamol, lactic acidosis, hypokalaemia, asthma

Salbutamol given by inhalation is considered first line treatment in the management of acute asthma presentations. Standard therapy also includes the use of corticosteroids and inhaled ipratropium bromide in moderate to severe asthma presentations. If response to this treatment is unsatisfactory then recourse to intravenous β₂-agonists is recommended. To date there are no published trials that establish the efficacy or safety of the combination of inhaled salbutamol and a continuous intravenous salbutamol infusion over inhaled salbutamol alone for treatment of severe acute asthma. However, theory as well as clinical observation suggests that the systemic actions of β₂-agonists may adversely affect patients with severe asthma. This article reviews the evidence for the use of intravenous β₂-agonists in asthma and looks at the systemic and metabolic effects and how they may be relevant to patients with acute severe asthma.

Does intravenous salbutamol work as a bronchodilator?

Intravenous salbutamol is efficacious as a bronchodilator. In a dose response study of intravenous salbutamol in 10 convalescent asthma patients, an infusion of 4.16 µg/min of salbutamol resulted in a significant rise in mean peak expiratory flow rate (PEFR) and FEV₁ at

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30 and 60 minutes. There was little further increase in FEV₁ and PEFR with increasing doses of salbutamol up to 25 μg/min. The authors thus recommended salbutamol infusions of 5 to 10 μg/min for the treatment of acute asthma.

A dose-response study of bolus injections of salbutamol in 10 patients demonstrated that optimal increases in PEFR (mean rise 48.8%) and FEV₁ (mean rise 40.4%) were seen after a dose of 200 μg of salbutamol. A comparison of 300 μg of salbutamol given intravenously as a bolus or as a 30 min infusion (10 μg/min) showed that both were equally efficacious in terms of increases in PEFR in 16 mild asthma patients. Fitchett et al, found a good response to an intravenous bolus of salbutamol in 6 of 12 episodes of severe asthma in a group of eleven asthma patients. The authors felt that an optimal effect was achieved with 300 μg and that intravenous salbutamol was safe.

**Intravenous or nebulised?**

Two large randomised controlled trials have been performed in an attempt to answer the question of whether nebulised or intravenous salbutamol is the better treatment in severe asthma presentations. Salmeron et al, performed a randomised, blinded, placebo controlled, multicentre study comparing nebulised salbutamol 10 mg over one hour with salbutamol 500 μg intravenous over an hour in 48 adults with hypercapnic acute asthma. The nebulised route was associated with significantly better responses in terms of clinical index score, PEFR and PaCO₂. There were more treatment successes with the nebulised treatment (19/22 vs 12/25). Blood levels of salbutamol were not significantly different between the two treatments. Hypokalaemia was seen in both groups but the absolute fall was greater for the intravenous group. The authors’ conclusion was that nebulised treatment was more efficacious and had fewer side effects than intravenous salbutamol.

The Swedish Society of Chest Medicine addressed the same question in a multicentre, randomised, open-label study that enrolled 176 adult patients with acute severe asthma (heart rate >100 beats per minute and PEFR < 50% predicted). Patients with very severe asthma were excluded (PEFR < 15% predicted). Eighty seven patients received 0.3 mg/kg salbutamol via a nebuliser in 2 divided doses over one hour whilst 89 patients received a 10 minute infusion of salbutamol 5 μg/kg. All patients received an aminophylline infusion after one hour. Parameters monitored were PEFR, heart rate and blood pressure in addition to monitoring of side effects such as nausea, headache, tremor and palpitations. The mean increase in PEFR was greater with nebulised route at 30 and 60 minutes. The nebulised group had significantly higher mean salbutamol blood levels at 55 and 90 minutes and, as might be expected, had more side effects such as tremor and palpitations. Patients receiving the nebulised treatment had greater improvement in their asthma, as assessed by a physician, than those receiving salbutamol by the intravenous route.

These studies can be criticised on the basis that they were of short duration and did not address issues such as time to discharge. In addition the Swedish study, although having large numbers, was not blinded and only had PEFR as an objective measure of response. The dose of intravenous salbutamol was modest in both studies in comparison to practice today, though the nebulised dose in the study of Salmeron et al, was also conservative. However, these are the only large studies to directly compare intravenous and nebulised salbutamol. Numerous smaller studies have also addressed this question with variable conclusions (Table 1). One possible reason for conflicting study outcomes is the variation in doses used. It has been suggested that if the ratio of the nebulised dose to the intravenous dose is greater or equal to 10:1 then the nebulised route is as good, or better, than the intravenous route.

**Effect of delivery route on blood levels**

There is significant systemic absorption of nebulised salbutamol. There was no significant difference in salbutamol blood levels between the intravenous and nebuliser groups in the study by Salmeron et al, whilst in the Swedish study, salbutamol levels were significantly higher in the nebulised group. Given the greater efficacy of the nebulised route, it appears that local effects are more important than blood levels in determining response to treatment. One of the rationales for using intravenous salbutamol is to achieve adequate blood levels in cases of severe asthma where bronchial obstruction is purported to prevent the nebulised drug from reaching the airways. Blood level data from these studies raises questions as to the validity of this rationale.

Janson et al, measured blood levels of β₂-agonist on patients with asthma presenting to the emergency department. There was a negative correlation between blood level and bronchodilation to 5 μg/kg of intravenous salbutamol. There was no such association seen in bronchodilator response to nebulised (0.15 mg/kg) salbutamol. This suggests a plateau effect in the dose response curve to intravenous salbutamol as has been suggested elsewhere. In a further study, Janson found that area under the curve (AUC) for blood levels following nebulised (0.15 mg/kg) and 5 μg/kg intravenous were similar although there was more...
Table 1. Studies where intravenous salbutamol was compared with nebulised salbutamol

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Trial type</th>
<th>Inhaled dose</th>
<th>i.v. dose</th>
<th>Outcome measures</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al</td>
<td>10</td>
<td>Prospective</td>
<td>Initial 5mg neb</td>
<td>200 µg after neb of 5mg</td>
<td>PEFR</td>
<td>i.v. successful where neb failed</td>
</tr>
<tr>
<td>Hetzel et al</td>
<td>5</td>
<td>Prospective</td>
<td>200 µg MDI</td>
<td>250 µg</td>
<td>PEFR, FVC, FEV₁, HR</td>
<td>Equivalent but i.v. more prolonged side effects</td>
</tr>
<tr>
<td>Neville et al</td>
<td>10</td>
<td>Randomised, PC, DB, XO</td>
<td>200 µg MDI</td>
<td>4 µg/kg bolus</td>
<td>FEV₁, FVC</td>
<td>Equivalent - i.v. more side effects</td>
</tr>
<tr>
<td>Lawford et al</td>
<td>16</td>
<td>Randomised, DB</td>
<td>10 mg neb</td>
<td>900 µg over 45min</td>
<td>PEFR, FEV₁, ABG, HR</td>
<td>Equivalent - i.v. more side effects</td>
</tr>
<tr>
<td>Bloomfield et al</td>
<td>22*</td>
<td>Randomised, DB, XO</td>
<td>neb dose unclear</td>
<td>500 µg bolus</td>
<td>PEFR, HR, PP, ABG</td>
<td>Equal in terms of PEFR, neb reduced PP more side effects</td>
</tr>
<tr>
<td>Cheong et al</td>
<td>76</td>
<td>Randomised</td>
<td>10 mg over 4 hours</td>
<td>12.5 µg/min for 4 hours</td>
<td>PEFR, HR</td>
<td>i.v. more efficacious but more side effects</td>
</tr>
<tr>
<td>Bohn et al</td>
<td>16</td>
<td>Prospective</td>
<td>0.03µg/kg initially + infusion</td>
<td>10 µg/kg stat infusion</td>
<td>Avoidance of ventilation</td>
<td>i.v. successful where neb failed</td>
</tr>
</tbody>
</table>

PC = placebo controlled, DB = double blind, XO = crossover, neb = nebulised, MDI = metered dose inhaler, PP = pulsus paradoxus, i.v. = intravenous, * = 22 episodes in 19 patients

variation in blood levels for the nebuliser group. Peak increase in PEFR and 90 minute AUC for PEFR was greater for nebulised than intravenous treatment, again indicating the importance of the local effect rather than systemic bioavailability for the bronchodilator response. These studies suggest that the nebulised route is at least as efficacious as the intravenous route when the two are compared directly. However, in current clinical practice intravenous therapy is often given in addition to the nebulised route, a practice for which there is no supporting evidence.

Browne et al, studied the effect of a bolus of intravenous salbutamol in addition to regular nebulised salbutamol. The study was a double blind, placebo controlled trial in 29 paediatric patients with acute severe asthma. Patients received salbutamol nebulisers every 20 minutes in addition to a 15 µg/kg bolus of salbutamol intravenous or placebo intravenous. Patients receiving an intravenous bolus of salbutamol (n = 14) had a more rapid recovery time in terms of need for frequent nebulisers, time to discharge from the emergency department and the need for supplemental oxygen. There was also a more rapid improvement in clinical severity score in the intravenous salbutamol group. There were no significant side effects. The authors felt that by giving the intravenous bolus early they took advantage of a small window of opportunity to prevent severe obstruction and subsequent resistance to nebulised treatment. It was suggested that the study of Salmeron et al gave the intravenous treatment too late to see this effect.

From these studies it is clear that the nebulised route should remain the initial route of therapy in acute asthma, as it is as least as effective as the intravenous route, it can achieve similar blood levels to the intravenous route, and it appears to have greater bronchodilator effects for a given blood level. Evidence to support or refute the practice of adding an intravenous infusion of salbutamol to regular intrhaled therapy is lacking. There is limited evidence that the addition of an initial intravenous salbutamol bolus to regular nebulised salbutamol may be of benefit. Any decision to add an intravenous salbutamol infusion to regular nebulised treatment should balance any potential benefit against the lack of supporting evidence for the practice and the potential side effects of systemic salbutamol.

Systemic effects
Salbutamol is known to affect carbohydrate metabolism, electrolytes, ventilation and the cardiovascular system in a predictable fashion. For equivalent bronchodilator effects intravenous salbutamol appears to have greater metabolic effects than nebulised salbutamol.

Glucose and insulin
Salbutamol causes hyperglycaemia by promoting glycogenolysis. This effect can be seen after intravenous, oral, and inhaled salbutamol. The onset is rapid, and is dose related. Serum insulin levels also rise due either to direct stimulation of islet cells, or in response to a rising serum glucose. However, the insulin rise tends to peak sooner than glucose and is inadequate for the observed rise in glucose resulting in persistent hyperglycaemia.
The slow rise in insulin has been attributed to fasting prior to presentation with acute asthma though it may be due to increased levels of fatty acids resulting from \( \beta_2 \)-stimulated lipolysis.\(^{26}\)

There is a tendency for the insulin levels to rise over a period of 12 to 24 hours with correction of hyperglycaemia even in the face of continued salbutamol infusion.\(^{26}\) Of concern is that in patients with diabetes, hyperglycaemia and insulin and relative insulin deficiency could result in diabetic ketoacidosis. Diabetic ketoacidosis has been reported on a number of occasions in the obstetric literature where \( \beta_2 \)-agonists are used to terminate premature labour.\(^{27-29}\) Whereas, otherwise well obstetric patients may be able to compensate for the acidosis by increasing minute ventilation, patients with severe asthma may not have the ventilatory reserve to do so. Concomitant use of corticosteroids in acute asthma may exacerbate hyperglycaemia and the risk of ketoacidosis.

**Potassium**

Salbutamol causes a fall in potassium that is rapid and dose related.\(^{24}\) The fall in potassium is reported to be due to a direct stimulation of Na/K-ATPase in muscle via \( \beta_2 \)-receptors which causes an intracellular potassium shift.\(^{19}\) This is insulin independent.\(^{19}\) There may also be an intracellular shift associated with the rise in glucose and insulin seen with salbutamol. Studies show that renal excretion of potassium falls with \( \beta_2 \)-agonists,\(^{30,31}\) supporting the theory that the hypokalaemia is due to a shift in body potassium rather than a fall in body stores. A transient rise in potassium occurs prior to the observed fall,\(^{23,24}\) and this has been ascribed to release of potassium from the liver.\(^{19}\) The transient rise seen has led to speculation that salbutamol may not be an appropriate treatment for severe hyperkalaemia.\(^{23}\) The hypokalaemic effect is dose related and is seen if sufficient salbutamol is given by the inhaled route.\(^{23}\) The hypokalaemic effect may be more prolonged for infusion compared to bolus intravenous salbutamol for equivalent cumulative doses.\(^4\) It is possible that low potassium may predispose to cardiac arrhythmias or cause muscle weakness.

**Lactate**

Serum lactate rises in response to \( \beta_2 \)-agonists as a result of \( \beta_2 \) stimulated anaerobic glycolysis in muscle.\(^{19,24}\) Serum lactate has been shown to rise with intravenous salbutamol,\(^{21,32}\) and has been reported to occur following nebulised salbutamol.\(^{33}\) There is a dose response effect with increasing doses of salbutamol causing increasing levels of lactate.\(^{24}\) If production exceeds hepatic clearance then lactic acidosis will ensue resulting in increased ventilatory demands. Harvey et al.,\(^{20}\) found no tolerance to intravenous salbutamol with respect to lactate production after regular inhaled \( \beta_2 \)-agonists in asthma patients although tolerance has been demonstrated in normals.\(^{32}\)

Salbutamol infusion has also been shown to cause a rise in free fatty acids,\(^{21,34}\) and falls in serum magnesium, phosphate and calcium.\(^{24}\) The significance of these changes is unclear, but coexistent hypomagnesaemia and hypokalaemia might predispose to cardiac arrhythmias.

**Cardiovascular effects**

Salbutamol has effects on both the heart and the systemic and pulmonary vasculature. A fall in vascular resistance due to vasodilation in skeletal muscle beds results in a fall in diastolic and mean arterial pressure.\(^{2,35,36}\) May et al., found that postural hypotension was common after intravenous injection.\(^7\) Salbutamol causes tachycardia,\(^{35,36}\) due to its direct action on cardiac \( \beta_2 \)-receptors and due to the reduction in afterload. The reduction in vascular resistance and tachycardia in addition to a direct inotropic effect on the heart\(^{19}\) results in an increase in cardiac output.\(^{35}\) These cardiovascular effects are much more prominent after intravenous administration. Systemic salbutamol prolongs QTc interval,\(^{36}\) due to cardiac \( \beta_2 \)-stimulation and also due to the hypokalaemia that results from systemic salbutamol. Salbutamol also causes pulmonary vasodilation,\(^{35}\) and as a result influences ventilation perfusion matching in the lung.\(^{37}\) Ballester et al.,\(^{37}\) found that intravenous salbutamol worsened ventilation perfusion matching in asthmatics. Arterial oxygenation did not fall however, due to the concomitant increase in cardiac output. No such effect was seen for a dose of inhaled salbutamol causing the same degree of bronchodilatation. This may be important in patients with limited cardiac reserve who cannot increase cardiac output and so may become more hypoxic with salbutamol. Giving salbutamol by the inhaled route with supplemental oxygen would minimise this risk.

The cardiovascular effects of salbutamol may adversely affect patients. The tachycardia observed with salbutamol may precipitate myocardial ischaemia in susceptible individuals due to the resultant increase in myocardial work and oxygen demand. This may be made worse by reduced oxygen delivery to the heart as a result of lowered mean blood pressure, shortened diastole and the pulmonary vascular dilation causing worsening ventilation perfusion matching. Changes in the QTc along with the reductions in serum magnesium and potassium may precipitate arrhythmias particularly in the setting of myocardial ischaemia. A recent meta-analysis showed that salbutamol use was associated with an increased risk of adverse cardiovascular events.
although the exact mechanisms where not elucidated. 38

**Metabolic rate**

Salbutamol has been shown to increase basal metabolic rate, 39 and to increase oxygen consumption (\(\dot{V}O_2\)) 40,41 and carbon dioxide production (\(\dot{V}CO_2\)). 41 The increased metabolic rate is due to \(\beta_2\) adrenergic stimulated glycolysis in liver and muscle. 39,24 Burdet and Schultz 42 found a mean increase in resting energy expenditure of 4.8% following 5 mg of nebulised salbutamol. The rise in metabolic rate occurred in spite of bronchodilation that should theoretically have reduced the work of breathing. Amoroso et al. 41 showed that inhaled salbutamol increased metabolic rate in a dose dependant manner. The respiratory exchange ratio was observed to increase reflecting ventilation in excess of metabolic needs which indicates that there was some other stimulus to ventilation above increased metabolic rate. There appears to be some tolerance to these metabolic effects with chronic \(\beta_2\)-agonist usage. 42

**The development of tolerance**

Chronic \(\beta_2\)-stimulation appears to attenuate the metabolic effects seen with acute salbutamol administration. Harvey 39 found that airway response and lactate production to salbutamol was unchanged but the hyperglycaemic response was attenuated by regular inhaled salbutamol. Holgate et al. 32 however, found that glucose, airway and lactate responses to salbutamol were attenuated after chronic \(\beta_2\)-inhalation. Richards et al. 43 found that in pregnant women receiving intravenous \(\beta_2\)-agonists for premature labour, lactate rose initially but found that over 24 hours the lactate production by the respiratory muscles with associated reduction in clearance due to liver hypoperfusion. They discounted \(\beta\)-agonists as the cause as the lactate levels were not measured. Nogradi et al. 34 found no tachyphalaxis to the metabolic effects of intravenous salbutamol during a single hospital admission for acute asthma.

Intravenous, 44 and inhaled steroids, 45 have been shown to rapidly restore \(\beta\)-receptor sensitivity in the lung and systemically. What affect steroids administered in the setting of acute asthma has on the metabolic responses of individuals taking \(\beta\)-agonists chronically is not known. It may be that the \(\beta_2\)-agonist naïve patient is more susceptible to the metabolic effects and that chronic asthma patients are protected by regular \(\beta_2\)-agonist use. However, this “protection” may be diminished by inhaled or parenteral corticosteroids.

**Respiration**

Salbutamol, 46,47 and isoprenaline, 47,48 have been shown to increase minute ventilation in man. Heistad et al demonstrated that isoprenaline increased minute ventilation but \(\dot{V}O_2\) and \(\dot{V}CO_2\) were not measured. 48 They also noted that \(PaCO_2\) fell with isoprenaline suggesting that the rise in ventilation was not just in response the increase in metabolic rate seen with \(\beta_2\)-agonists. 39,41 However lactate and pH were not recorded, so it is unclear whether the fall in \(PaCO_2\) was due to a metabolic acidosis with bicarbonate buffering or to direct stimulation of chemoreceptors. Lundhom et al. 49 demonstrated a rise in \(Ve\), \(\dot{V}O_2\) and \(\dot{V}CO_2\) with intravenous adrenaline. The \(\dot{V}CO_2\) rose by about 50% from baseline and was greater than the rise in \(\dot{V}O_2\) indicating ventilation in excess of metabolic needs. Lactate was observed to rise and bicarbonate fell. It was calculated that about half of the rise in \(\dot{V}CO_2\) was due to increased metabolic rate with the remainder due to acidosis and bicarbonate buffering from increased lactate and free fatty acid production. Given that adrenaline and salbutamol have similar metabolic effects with respect to glycolysis and lactate production it is likely that salbutamol increases ventilation in a similar way. The increase in respiratory exchange ratio observed by Amoroso et al. 41 following salbutamol is consistent with this.

**Metabolic acidosis in asthma**

Metabolic acidosis has been noted to occur in a proportion of patients with acute asthma. A number of theories exist as to the cause for this. Appel et al. 50 ascribed an observed lactic acidosis in asthma patients that had received subcutaneous adrenaline to increased production by the respiratory muscles with associated reduction in clearance due to liver hypoperfusion. They discounted \(\beta\)-agonists as the cause as the lactate levels were higher than seen in experimental studies and the lactate levels decreased in spite of continued treatment. The mean lactate level was 4.5 mmol/L a level similar to that seen in patients in premature labour receiving intravenous \(\beta\)-agonists. 31 Okrent et al. 51 found lactate elevation was not common in asthma and suggested that the metabolic acidosis seen was non-anion gap in nature due to renal bicarbonate wasting.

Mountain et al. 52 thought that the lactic acidosis of asthma was multifactorial with possible causes including increased production due to respiratory alkalosis, 53 and increased work of breathing with hypoxia. Roncoroni et al. 54 who found that 25 of 39 patients admitted with asthma had a raised lactate reached similar conclusions. Postulated causes of the high lactate were increased production due to work of breathing, reduced lactate metabolism due to hepatic engorgement and alkalosis. Rabbet et al. 55 studied 29 patients admitted to their ICU for asthma and found that 17/29 had an elevated lactate on arrival and that all
subsequently developed a lactic acidosis. All received parenteral \(\beta_2\)-agonists in ICU. Mean lactate rise from ICU admission was 4.6 mmol/L with a mean peak of 7.72 mmol/L.

Alkalosis is an unlikely cause of the rise in lactate production. Alkalosis typically produces lower lactate levels than seen in acute asthma patients, and an alkalosis of the order required would be uncommon in severe asthma. Eldridge studied the effect of hyperventilation and increased workload on serum lactate in normals. A 21 cmH\(_2\)O inspiratory load and increased dead space resulting in a minute ventilation of 21 litres did not increase serum lactate. When repeated whilst breathing 15% oxygen, lactate rose significantly but only to a mean of 1.02 mmol/L. It is thus unlikely that increased work of breathing and mild hypoxia is the sole explanation for the levels of lactate seen in severe asthma.

Several reports in the literature have appeared suggesting that salbutamol induced increases in lactate may be clinically relevant. Maury et al. reported a case of a 65 year-old man who developed a severe acidosis due to inappropriate escalation of asthma treatment. He was given 20 mg of nebulised salbutamol over 3 hours but became progressively more breathless. As a consequence he was given intravenous salbutamol. He became more distressed and blood gases showed a lactic acidosis with a lactate level of 10 mmol/L. He improved with cessation of all \(\beta_2\)-agonists and treatment with regular ipratropium bromide. Cases of acidosis associated with the use of inhaled isoprenaline and inhaled salbutamol have also been reported.

**Clinical implications**

The increased ventilatory demands from the rise in metabolic rate and lactate production due to systemic salbutamol has important implications for patients with severe asthma. In severe asthma, systemic salbutamol will impose increased demands on a respiratory system with little or no reserve. If asthma persists despite initial salbutamol therapy, these demands must be met by a respiratory system compromised by airflow obstruction and hyperinflation. The increased work of breathing associated with efforts to increase minute ventilation may lead to increasing respiratory distress. As respiratory rate increases to meet the increased demand, inspiratory time will be reduced worsening dynamic hyperinflation. Dynamic hyperinflation places the respiratory muscles at a mechanical disadvantage promoting fatigue. Dynamic hyperinflation also results in intrinsic PEEP (PEEP) that imposes an inspiratory threshold load, increasing work of breathing and further promoting muscle fatigue. PEEP, also potentially impairs right and left ventricular function.

With the increased demand and abnormal mechanics respiratory rate will rise, increasing dead space ventilation so causing carbon dioxide levels to rise. This further worsens respiratory distress and may contribute to respiratory muscle failure. Ultimately the increased ventilatory demands, worsening lung mechanics and acidosis may result in fatigue and respiratory failure. Salbutamol induced hypokalaemia may further contribute to respiratory muscle dysfunction and respiratory failure (Figure 1). Failure by clinicians to appreciate these possibilities may lead to inappropriate escalation of \(\beta_2\)-agonists that may paradoxically worsen the situation. That this is not just a theoretical concern is supported by a number of case reports describing this situation in clinical practice.

**Recommendations**

Patients presenting with severe asthma should receive salbutamol and ipratropium bromide by inhalation in addition to parenteral steroids and oxygen. There is little evidence to support the use of intravenous salbutamol infusions. The study in children by Browne suggests it would be reasonable to consider an initial bolus of intravenous salbutamol in severely unwell patients, at the time of presentation if they have not already had a significant trial of inhaled salbutamol.

If there is failure to respond to treatment or an apparent worsening of asthma then reassessment of the patient is mandatory prior to escalation of nebulised \(\beta_2\)-agonist treatment. A clinical assessment of the degree of airflow obstruction should be made as well as an assessment for other pathology such as pneumothorax. It is important to note that increased heart and respiratory rate may reflect treatment side effects rather than worsening asthma. Blood for arterial blood gases, serum lactate, potassium and glucose should be taken. If a metabolic acidosis is present then the possibility of a treatment side effect needs to be entertained and considered given to a reducing or ceasing \(\beta_2\)-agonist use rather than further escalation.

If breathlessness is truly due to severe asthma then consideration should be given to therapies that work via alternate mechanisms to \(\beta_2\)-agonists. Non-invasive ventilation appears to be of benefit in acute severe asthma by reducing the work of breathing. This reduces dyspnoea and consequently respiratory rate falls, reducing dynamic hyperinflation. This may stabilise the patient whilst waiting for parenteral corticosteroids to take effect. Inhaled steroids may also be of benefit in acute asthma by decreasing mucosal oedema, and sensitising \(\beta_2\)-receptors. There is also growing evidence to support the use of magnesium in severe asthma.

If a decision is made to use an intravenous infusion
of salbutamol in a non-ventilated asthma patients, then lactate, glucose, potassium and blood gases should be monitored one to 2 hourly for the first 4 hours and then 6 hourly for the first 24 hours. The development of a metabolic acidosis in a patient with severe asthma that is not mechanically ventilated is a strong indication to reconsider the use of parenteral $\beta_2$-agonists.

**Conclusion**

Systemic salbutamol has metabolic effects that may worsen respiratory function in asthma. The evidence presented above suggests salbutamol should not be given by intravenous infusion to asthma patients outside of clinical trials. Patients who appear unresponsive to nebulised $\beta_2$-agonists should have blood gasses performed to exclude paradoxical worsening of breathlessness due to the metabolic effects of salbutamol. For patients who fail to respond to inhaled $\beta_2$-agonists, ipratropium and systemic steroids, consideration should be given to other therapies such as non-invasive ventilation rather than increasing the dose of a drug that may paradoxically worsen respiratory function.

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