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 β_2-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. β_2-agonists have numerous systemic actions that may adversely affect patients with severe respiratory compromise. The most important of these is the potential for β_2-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 β_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* (**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.[1] Standard therapy also includes the use of corticosteroids and inhaled ipratropium bromide in moderate to severe asthma presentations.[1] If response to this treatment is unsatisfactory then recourse to intravenous β_2-agonists is recommended.[1] 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 β_2-agonists may adversely affect patients with severe asthma. This article reviews the evidence for the use of intravenous β_2-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 FEV_1 at

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30 and 60 minutes.[2] There was little further increase in FEV_1 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 FEV_1 (mean rise 40.4%) were seen after a dose of 200 µg of salbutamol.[3] 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.[4] 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.[5] 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.[6] The nebulised route was associated with significantly better responses in terms of clinical index score, PEFR and $PaCO_2$. 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).[7] 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.[15]

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,[7] salbutamol levels were significantly higher in the nebulised group. Given the greater efficacy of the nebulised route,[6] 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.[8] Blood level data from these studies,[6,7] raises questions as to the validity of this rationale.

Janson *et al*, measured blood levels of β_2-agonist on patients with asthma presenting to the emergency department.[16] 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.[2] 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

Author	*n*	*Trial type*	*Inhaled dose*	*i.v. dose*	*Outcome measures*	*Conclusion*
Williams *et al*[8]	10	Prospective	Initial 5mg neb	200 μg after neb of 5mg	PEFR	i.v. successful where neb failed
Hetzel *et al* [9]	5	Prospective	200 μg MDI	250 μg	PEFR, FVC FEV_1, HR	Equivalent but inhaled response more prolonged
Neville *et al* [10]	10	Randomised, PC, DB, XO	200 μg MDI	4 μg /kg bolus	FEV_1, FVC	Equivalent - i.v. more side effects
Lawford *et al* [11]	16	Randomised, DB	10 mg neb	900 μg over 45min	PEFR, FEV_1, ABG, HR	Equivalent - i.v. more side effects
Bloomfield *et al* [12]	22*	Randomised, DB, XO	neb dose unclear	500 μg bolus	PEFR, HR, PP, ABG	Equal in terms of PEFR, neb reduced PP more
Cheong *et al* [13]	76	Randomised	10 mg over 4 hours	12.5 μg/min for 4 hours	PEFR, HR	i.v. more efficacious but more side effects
Bohn *et al* [14]	16	Prospective	0.03ug/kg initially	10 μg /kg stat + infusion	Avoidance of ventilation	i.v. successful where neb failed

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.[17]

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.[18] 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*,[6] 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,[6, 17] and it appears to have greater bronchodilator effects for a given blood level.[6,17] Evidence to support or refute the practice of adding an intravenous infusion of salbutamol to regular inhaled therapy is lacking. There is limited evidence that the addition of an initial intravenous salbutamol bolus to regular nebulised salbutamol may be of benefit.[18] 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.[10]

Glucose and insulin

Salbutamol causes hyperglycaemia by promoting glycogenolysis.[19] This effect can be seen after intravenous,[10,20,21] oral,[22] and inhaled salbutamol.[10,23] The onset is rapid,[10,23,24] and is dose related.[24] Serum insulin levels also rise,[10,24] due either to direct stimulation of islet cells,[25] 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.[24]

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 β_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 relative insulin deficiency could result in diabetic ketoacidosis. Diabetic ketoacidosis has been reported on a number of occasions in the obstetric literature where β_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 β_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 β_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 β_2-agonists as a result of β_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 β_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 hypomagnasaemia 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.[2] Salbutamol causes tachycardia,[35,36] due to its direct action on cardiac β_1-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[36] results in an increase in cardiac output.[35] These cardiovascular effects are much more prominent after intravenous administration[35]. Systemic salbutamol prolongs QT_c interval,[36] due to cardiac β_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 QT_c 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 ($\dot{V}O2$)[40,41] and carbon dioxide production ($\dot{V}CO_2$).[41] The increased metabolic rate is due to β_2 adrenergic stimulated glycolysis in liver and muscle.[19,24] Burdet and Schultz,[39] 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 β_2-agonist usage.[42]

The development of tolerance

Chronic β_2-stimulation appears to attenuate the metabolic effects seen with acute salbutamol administration. Harvey[20] 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 β_2-inhalation. Richards *et al*,[43] found that in pregnant women receiving intravenous β_2-agonists for premature labour, lactate rose initially but found that over 24 hours the lactate levels tended to return to normal in spite of continued β_2-agonist infusion. Nogrady *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 β-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 β-agonists chronically is not known. It may be that the β_2-agonist naïve patient is more susceptible to the metabolic effects and that chronic asthma patients are protected by regular β_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 β_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 $\dot{V}e$, $\dot{V}O_2$ 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 β-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 β-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. Rabbat *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 β_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.[53] Alkalosis typically produces lower lactate levels than seen in acute asthma patients,[55] and an alkalosis of the order required would be uncommon in severe asthma. Eldridge[56] studied the effect of hyperventilation and increased workload on serum lactate in normals. A 21 cmH_2O 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*,[57] 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 β_2-agonists and treatment with regular ipratropium bromide. Cases of acidosis associated with the use of inhaled isoprenaline[58] and inhaled salbutamol have also been reported.[33,59]

Clinical implications

The increased ventilation resulting 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, expiratory time will be reduced worsening dynamic hyperinflation. Dynamic hyperinflation places the respiratory muscles at a mechanical disadvantage promoting fatigue.[60] Dynamic hyperinflation also results in intrinsic PEEP ($PEEP_i$) that imposes an inspiratory threshold load, increasing work of breathing and further promoting muscle fatigue.[61] $PEEP_i$ also potentially impairs right and left ventricular function.[61] 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.[62] 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[63] (Figure 1). Failure by clinicians to appreciate these possibilities may lead to inappropriate escalation of β_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.[57,59,64]

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 *et al*,[18] 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 β_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.[11] 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 consideration given to a reducing or ceasing β_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 β_2-agonists. Non-invasive ventilation appears to be of benefit in acute severe asthma,[65] by reducing the work of breathing.[66] This reduces dyspnoea and consequently respiratory rate falls,[65] 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,[67] by decreasing mucosal oedema,[68] and sensitising β_2-receptors.[45] There is also growing evidence to support the use of magnesium in severe asthma.[69, 70]

If a decision is made to use an intravenous infusion

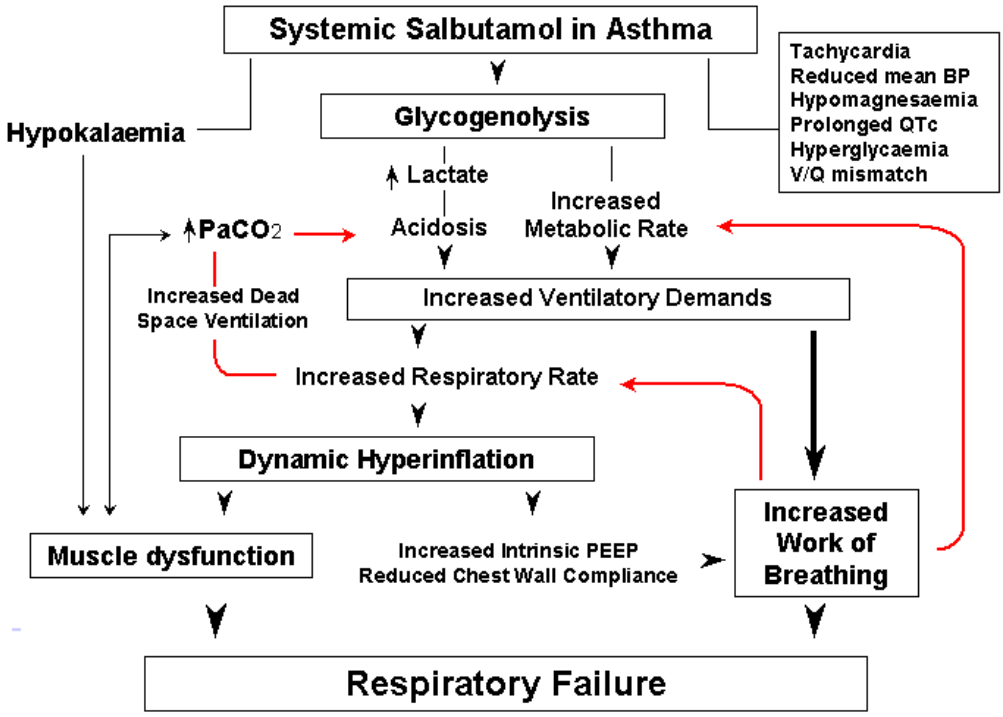

Figure 1. Clinical implications of systemic salbutamol

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 β_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 β_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 β_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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REFERENCES

1. National Asthma Council Australia. Asthma management handbook 2002. National Asthma Council Australia, Melbourne [online; cited March 12004] Available from: http://www.nationalAsthma.org.au.
2. May C, Paterson J, Spiro S, Johnson A. Intravenous infusion of salbutamol in the treatment of asthma. Br J Clin Pharmacol 1975;2:503-508.
3. Spiro S, May C, Johnson J, Paterson J. Intravenous injection of salbutamol in the management of asthma. Thorax 1975;30:236.
4. Elegbeleye O, Williams K, Femi-Pearse D. Comparison of the metabolic effects of salbutamol administered in a one minute bolus and a continuous infusion in patients with bronchial asthma. Israel J Med Sci 1978;14;455-458.
5. Fitchett D, McNicol M, Riordan J. Intravenous salbutamol in management of status asthmaticus. Br Med J 1975;1:53-55.
6. Salmeron S, Brochard L, Mal H, Tenaillon A, Henry-Amar M, Renon D, Duroux P, Simonneau G. Nebulized versus intravenous albuterol in hypercapnic acute asthma. Am J Respir Crit Care Med 1994;149:1466-1470.
7. Swedish Society of Chest Medicine. High dose inhaled versus intravenous salbutamol combined with theophylline in severe acute asthma. Eur Respir J 1990;3:163-170.
8. Williams S, Seaton A. Intravenous or inhaled salbutamol in severe asthma? Thorax 1977;32:555-558.

9. Hetzel M, Clark T. Comparison of intravenous and aerosol salbutamol. Br Med J 1979;2:919.
10. Neville A, Palmer J, Gaddie J, May C, Palmer K, Murchison L. Metabolic effects of salbutamol: comparison of aerosol and intravenous administration. Br Med J 1977;1:413-414.
11. Lawford P, Jones B, Milledge J. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. Br Med J 1976;1:84.
12. Bloomfield P, Carmicheal J, Petrie G, Jewell N, Crompton G. Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life threatening asthma. Br Med J 1979;1:848-850.
13. Cheong B, Reynolds S, Rajan G, Ward M. Intravenous β agonist in severe acute asthma. Br Med J 1988;297:448-450.
14. Bohn D, Kalloghilian A, Jenkins J, Edmonds J, Barker G. Intravenous salbutamol in the treatment of status asthmaticus in children. Crit Care Med 1984;12;10:892-895.
15. Noseda A, Yernault J. Sympathomimetics in acute severe asthma: inhaled or parenteral, nebulizer or spacer. Eur Respir J 1989;2:377-382.
16. Janson C, Boe J, Boman G, Mossberg B, Svedmyr N. Bronchodilator intake and plasma levels on admission for severe acute asthma. Eur Respir J 1992;5:80-85.
17. Janson C. Plasma levels and effects of salbutamol after inhaled or intravenous administration in stable asthma. Eur Respir J 1991;4:544-550
18. Browne GJ, Penna A, Phung X, Soo M. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. Lancet 1997;349:301-305.
19. Haffner CA, Kendall MJ. Metabolic effects of β2-agonists. J Clin Pharm Ther 1992;17:155-164.
20. Harvey JE, Baldwin CJ, Wood PJ, Alberti KG, Tattersfield AE. Airway and metabolic responsiveness to intravenous salbutamol in asthma: effect of regular inhaled salbutamol. Clin Sci 1981;60:579-585.
21. Goldberg R, van As M, Joffe BI, Krut L, Bersohn I, Seftel HC. Metabolic responses to selective β-selective stimulation in man. Post Med J 1975;51:53-58.
22. Wheeldon N, McDevitt D, McFarlane L, Lipworth B. β-Adrenoreceptor subtypes mediating metabolic effects of BRL 35135 in man. Clin Sci 1994;86:331-337.
23. Mandelberg A, Krupnik Z, Houri S, Smetana S, Gilad E, Matas Z, Priel IE. Salbutamol metered-dose inhaler with spacer for hyperkalemia. How Fast? How safe? Chest 1999;115:617-622.
24. Phillips PJ, Vedig AE, Jones PL, Chapman MG, Collins M, Edwards JB, Smeaton TC, Duncan BM. Metabolic and cardiovascular side effects of the B2-adrenoceptor agonists salbutamol and rimiterol. Br J Clin Pharmacol 1980;9:483-491.
25. Berend N, Marlin G. Characterization of β-adrenoceptor subtype mediating the metabolic actions of salbutamol. Br J Clin Pharmacol 1978;5:207-211.
26. Smith A, Banks J, Buchanan K, Cheohg B, Gunawardena K Mechanisms of abnormal glucose metabolism during treatment of severe asthma. QJM 1992 297:71-80.
27. Thomas D, Gill B, Brown P, Stubbs W. Salbutamol-induced diabetic ketoacidosis. Br Med J 1977;2:438.
28. Leslie D, Coats P. Salbutamol-induced diabetic ketoacidosis. Br Med J 1977;2:768.
29. Schilthuis M, Aarnoudse J. Fetal death associated with severe ritodrine induced ketoacidosis. Lancet 1980;1:1145.
30. Leitch A, Clancy L, Costello J, Flenley D. Effect of intravenous infusion of salbutamol on ventilatory response to carbon dioxide and hypoxia and on heart rate and plasma potassium in normal men. Br Med J 1976;1:365-367.
31. Braden G, von Oeyen P, Smith M, Germain M, Watson D, Haag B. Ritodrine- and terbutaline -induced hypokalaemia in preterm labor: mechanisms and consequences. Kidney Int 1997;51;6:1867-1875.
32. Holgate S, Stubbs, Wood P, McCaughey E, Alberti K, Tattersfield A. Airway and metabolic resistance to intravenous salbutamol: a study in normal man. Clin Sci 1980;59:155-161.
33. Assadi F. Therapy of acute bronchospasm complicated by lactic acidosis and hypokalemia. Clin Pediatr 1989;28;6:258-260.
34. Nogrady S, Hartley J, Seaton A. Metabolic effects of intravenous salbutamol in the course of acute severe asthma. Thorax 1977;32:559-562.
35. Aherns C, Smith G. Albuterol:an adrenergic agent for use in the treatment of asthma pharmacology, pharmacokinetics and clinical use. Pharmacotherapy 1984 4;3:105-120.
36. Bremmer P, Woodman K, Burgess C, Crane J, Purdie G, Pearce N, Beasley R. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. Eur Respir J 1993;6:204-210.
37. Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. Thorax 1989;44:258-267.
38. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest 2004;125:2309-2321.
39. Burdet L, Schultz Y Thermogenic effect of bronchodilators in patients with chronic obstructive pulmonary disease. Thorax 1997;52:130-135.
40. Newth C, Asmler B, Anderson G, Morley J. The ventilatory and oxygen costs in the anesthetized Rhesus monkey of inhaling drugs used in the therapy and diagnosis of asthma. Am Rev Respir Dis 1991;143:766-771.
41. Amoroso P, Wilson S, Moxham J, Ponte J. Acute effects of inhaled salbutamol on the metabolic rate of normal subjects. Thorax 1993;48:882-885.
42. Wilson S, Amoroso P, Moxham J, Ponte J. Modification of the thermogenic effect of acutely inhaled salbutamol by chronic inhalation in normal subjects. Thorax 1993;48:886-889.

43. Richards S, Chang F, Stempel L. Hyperlactacidemia associated with acute ritodrine infusion. Am J Obstet Gynecol 1983;146:1-5.
44. Tan K, Grove A, McLean A, Gnosspelius Y, Hall I, Lipworth B. Systemic corticosteroid rapidly reverses bronchodilator subsensitivity induced by formoterol in asthmatic patients. Am J Resp Crit Care Med 1997;156:28-35.
45. Aziz I, Lipworth B. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and β2-adreniceptor down regulation after regular-inhaled formoterol. Chest 1999;15:623-628.
46. Morice A, Schofield P, Keal E, Sever P. A comparison of the ventilatory, cardiovascular and metabolic effects of salbutamol, aminophylline and vasoactive intestinal peptide in normal subjects. Br J Clin Pharmacol 1986;22:149-153.
47. Warrell D, Robertson D, Newton Howes J, Conaolly M, Patterson J, Beilin L, Dollery C. Comparison of cardiorespiratory effects of isoprenaline and salbutamol in patients with bronchial asthma. Br Med J 1970;1:65-70.
48. Heistad D, Wheeler R, Mark A, Schmid P, Abboud F. Effects of adrenergic stimulation on ventilation in man. J Clin Invest 1972; 51:1469-1475.
49. Lundholm L, Svedmyr N. Studies on the stimulating effects of adrenaline and noradreanaline on respiration in man. Acta Physiol Scand 1966;67:65-75.
50. Appel D, Rubinstein R, Schrager K, Wiliams M. Lactic acidosis in severe asthma. Am J Med 1983;75:580-584.
51. Okrent D, Tessler S, Twersky R, Tashkin D. Metabolic acidosis not due to lactic acidosis in patients with severe acute asthma. Crit Care Med 1987;15:1098-1101.
52. Mountain R, Heffner J, Bracjett N, Sahn S. Acid-base disturbances in acute asthma. Chest 1990;98:651-655.
53. Relman A. Metabolic consequences of acid base disorders. Kidney International 1972;1:347-359.
54. Roncoroni A, Adrogue H, De Obrutsky C, Marchisio M, Herrera M. Metabolic acidosis in status asthmaticus. Respiration 1976;33:85-94.
55. Rabbat A, Laaban J, Boussairi A, Rochemaure J. Hyperlactatemia during acute severe asthma. Intens Care Med 1998;24:304-12
56. Eldridge F. Anaerobic metabolism of the respiratory muscles. J Appl Physiol 1966;21;3:853-857.
57. Maury E, Ioos V, Lepecq B, Guidet B, Offenstadt G. A paradoxical effect of bronchodilators. Chest 1997;111:1766-1767.
58. Braden G, Johnston S, Germain M, Fitzgibbons J, Dawson J. Lactic acidosis associated with the therapy of acute bronchospasm. N Engl J Med 1985;313:890.
59. Prakash S, Mehta S. Lactic acidosis in asthma: report of two cases and a review of the literature. Can Respir J 2002;9:203-208.
60. Macklem PT. Hyperinflation. Am Rev Respir Dis 1984;129:1-2.
61. Ranieri VM, Dambrosio M, Brienza N. Intrinsic PEEP and cardiopulmonary interaction in patients with COPD and acute ventilatory failure. Eur Respir J 1996;9:1283-1292.
62. Juan G, Calverley P, Talamo C, Schnader J, Roussos C. Effect of carbon dioxide on diaphragmatic function in human beings. N Engl J Med 1984;310:111-122.
63. Davies RG, Gemmell L. Severe hypokalaemia causing acute respiratory failure. Anaesth 2001;56:694.
64. Tobin AE, Santamaria JD. Respiratory failure precipitated by salbutamol. Intern Med J 2005;35:199-206.
65. Meduri G, Cook T, Turner R, Cohen M, Leeper K. Noninvasive positive pressure ventilation in status asthmaticus. Chest 1996;110:767-774.
66. Appendini L, Patessio A, Zanboni S, Carone M, Gukov B, Donner C, Rossi A. Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:1069-1076.
67. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. Am J Respir Crit Care Med 1998;157:698-703.
68. McFadden E. Inhaled glucocorticoids and acute asthma. Am J Respir Crit Care Med 1998; 157:677-678.
69. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child 2005; 90:74-77.
70. Silverman RA, Osborn H, Runge J, Gallagher EJ, Chiang W, Feldman J, Gaeta T, Freeman K, Levin B, Mancherje N, Scharf S; Acute Asthma/Magnesium Study Group. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. Chest 2002;122:489-497.