CASE REPORT

Conundrum in an asthma exacerbation

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SUMMARY

A 66-year-old man, an asthmatic, presented with symptoms suggestive of an acute exacerbation of asthma. His arterial blood gas revealed type 1 respiratory failure ($\text{PaO}_2 < 8 \text{ kPa}$ or 60 mm Hg with normal or low PaCO_2) with a compensated lactic acidosis. He was treated for an asthma exacerbation and sepsis. Despite treatment, his respiratory rate remained elevated although his hypoxaemia improved. There was progressive worsening of the lactic acidosis. Treatment for sepsis was augmented. Peak flow measurements were not used to assess the severity of his exacerbation nor his response to treatment. An alternate diagnosis of acute coronary syndrome with acute pulmonary oedema was made and his asthma treatment was stopped. This coincided with a decline in his serum lactate. A diagnosis of salbutamol-induced lactic acidosis (SILA) was made. SILA is a relatively common complication of salbutamol therapy in moderate/severe asthma exacerbations. It is caused by a mechanism different from the lactataemia that is associated with septic shock and life-threatening asthma.

BACKGROUND

Elevated lactate is a marker of severe sepsis and systemic shock. It is also seen in life-threatening asthma when respiratory fatigue and hypoxaemia become overwhelming. However, these are not the only causes. Repeated treatment with nebulised β -2 agonists in otherwise healthy patients can result in hyperlactataemia during a moderate/severe asthma exacerbation.

Acute asthma exacerbations are common medical presentations. Failure to recognise the described scenario can lead to unnecessary escalation of treatment and paradoxical worsening of symptoms (figure 1). Prompt recognition and management lead to dramatic improvement, reducing the risk of iatrogenic harm and prolonged hospital admission.

CASE PRESENTATION

The patient, a 66-year-old asthmatic man, had a 3-day history of worsening cough, wheeze and shortness of breath that was not relieved by his salbutamol inhaler. He had purulent sputum but neither fever, chest pain nor haemoptysis. He had been diagnosed with asthma many years ago, but was only treated with a salbutamol inhaler, which he used infrequently. He did not measure his peak flow. He had an admission for an asthma exacerbation 15 years prior, but had never required admission to intensive care. His other comorbidities were atrial fibrillation (AF) and a deep vein thrombosis many years earlier. He had never smoked. He was

a retired accountant. He took warfarin in addition to his salbutamol.

On examination, he was able to complete sentences, but was using his accessory muscles to aid respiration. He had a respiratory rate of 23 breaths/min and required 2 L/min of oxygen by nasal cannula to saturate at 94%. His heart rate was 104 bpm and he was normotensive and euvolaemic. Auscultation of the chest revealed a bilateral polyphonic wheeze. The remainder of the examination was normal. A clinical diagnosis of acute infective exacerbation of bronchial asthma was made.

INVESTIGATIONS

The patient's chest radiograph was normal. The white cell count was 11.3 (neutrophils 7.8 , eosinophils $0.03 \times 10^9/\text{L}$) and C reactive protein was 6 mg/dL . Renal function, serum electrolytes and liver enzymes were normal. Troponin was 8 ng/L . International normalized ratio was 2.2 . Arterial blood gas (ABG) at admission (table 1) revealed type 1 respiratory failure and a compensated metabolic acidosis, with a serum lactate of 5.6 mmol/L . Peak flow measurements were not taken. ECG showed AF with a controlled ventricular rate.

DIFFERENTIAL DIAGNOSIS**Treatment and course**

The patient received repeated doses of 5 mg nebulised salbutamol provided by the ambulance crew. In the emergency department, he received nebulised bronchodilators, parenteral steroids and magnesium. A sepsis care bundle was instituted (intravenous co-amoxiclav, intravenous fluids, blood culture, hourly urine output) because of the lactataemia and he was moved to a monitored bed in the acute medical unit, with instructions to staff to carry out overnight medical review.

He was reviewed 4 h and 6 h after admission. His respiratory rate remained elevated at 24/min but his oxygen saturations had improved to 99%. His heart rate was 105 bpm and he remained normotensive. Urine output was over 150 mL/h . Repeat ABGs revealed worsening lactataemia and metabolic decompensation (table 1). Peak flows were not recorded. Aminophylline infusion was prescribed and intravenous fluids were sped up. Nebulised salbutamol was continued.

After a further 2 h, he developed orthopnoea and worsening hypoxaemia but his wheeze had improved. Clinically, he was thought to have pulmonary oedema, probably precipitated by an acute coronary syndrome. Repeat ECG showed sinus tachycardia without ST changes. Repeat troponin was 40 ng/L . His chest radiograph was unchanged. Aminophylline and salbutamol were stopped. He

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Figure 1 Flow chart depicting the sequence of events with likely explanations.

was treated with fondaparinux, clopidogrel and a glyceryl trinitrate infusion.

At 10 h after admission, the patient showed signs of clinical improvement. His lactate had fallen to 5.9. Over the next few hours, his oxygen was weaned off and a serum lactate level was recorded at 3.3 mmol/L. A diagnosis of salbutamol-induced lactic acidosis and acute exacerbation of asthma was made. He was given prednisolone and a corticosteroid/long-acting β -2 agonist inhaler. Troponin fell to 24 ng/L and treatment for acute coronary syndrome was stopped. Echocardiogram showed a left ventricular ejection fraction of 65%, no regional wall motion abnormalities and no valvular pathology. He was discharged after 24 h.

OUTCOME AND FOLLOW-UP

At 3-month outpatient follow-up, the patient was well. He had no further asthma exacerbations. He required only infrequent inhaled salbutamol in addition to his salmeterol and fluticasone preventer medication. Infrequent salbutamol usage is not associated with lactic acidosis in otherwise healthy people.

DISCUSSION

Hyperlactataemia represents a disruption in the homeostatic control of lactate metabolism. It is caused either by increased lactate production or diminished lactate utilisation and clearance. The commonest cause of a raised serum lactate level is type 'A' lactic acidosis. This is associated with tissue hypoxia,

Table 1 Timeline of first 10 h of admission, detailing ABG results and medication administration (units and normal ranges for blood gas values given in parenthesis)

Time from presentation (hours)	0	4	5.5	6	10
Supplemental oxygen	2 L/min NC	2 L/min NC	4 L/min NC	4 L/min NC	35% FM
ABG					
pH (7.35–7.45)	7.39	7.34	7.29	7.32	7.37
PCO ₂ (kPa/mm Hg) (4.5–6/35–45)	4.46/33	4.86/36	4.78/36	3.88/29	4.48/34
PO ₂ (kPa/mm Hg) (10.6–13.3/80–100)	7.59/57	14.89/112	21.13/158	12.24/92	9.07/68
HCO ₃ (mmol/L) (22–26)	19.6	19	16.7	14.7	18.7
BE (mmol/L) (–2 to +2)	–4.6	–5.8	–8.7	–10.1	–5.8
Lactate (mmol/L) (<2)	5.6	7.2	9.2	11.1	5.9
Medication					
Nebulised salbutamol	Started and continued regularly			Stopped	
IV fluids	Slow infusion	Aggressive fluid boluses		Stopped	
Aminophylline Infusion		Started		Stopped	
GTN infusion				Started	Stopped

ABG, arterial blood gas; BE, base excess; FM, face mask; GTN, glyceryl trinitrate; IV, intravenous; NC, nasal cannula.

Table 2 Causes of lactic acidosis (adapted from Kraut JA *et al*¹)

Type of lactataemia	Mechanism	Causes
Type 'A' lactic acidosis	Tissue hypoxia, increased anaerobic metabolism, increased lactate production	Cardiogenic or hypovolaemic shock Severe sepsis Severe hypoxaemia Carbon monoxide poisoning Severe anaemia (<5 g/dL) Vigorous activity/generalised seizure Trauma
Type 'B' lactic acidosis	Increased aerobic glycolysis and pyruvate production	β -2 adrenergic stimulation (salbutamol) Cocaine abuse Pheochromocytoma Metformin (also suppresses hepatic gluconeogenesis) Linezolid Propofol Nucleoside reverse transcriptase inhibitors Cyanide Salicylates Liver disease
	Interference with oxidative phosphorylation	
	Impaired lactate clearance and metabolism	
	Increased glycolytic activity, tumour tissue hypoxia	Solid tumours, lymphoma, leukaemia
	Impairment of pyruvate dehydrogenase activity	Thiamine deficiency
	Multifactorial	Diabetes mellitus Acquired immunodeficiency disease

anaerobic metabolism and increased lactate production. It is seen in profound shock, severe sepsis and life-threatening asthma. However, there are a number of other causes of hyperlactataemia and these are unrelated to tissue hypoxia. Type 'B' lactic acidosis has a number of different causes. This topic has been extensively reviewed recently.¹ Table 2 summarises the main causes of lactic acidosis.

Salbutamol is a selective short acting β -2 agonist that has been used in the treatment of asthma exacerbations since the early 1970's. It has a systemic effect and is recognised as a cause of type 'B' lactic acidosis.² Intravenous salbutamol is most likely to cause this effect, but it is recognised with nebulised therapy^{2 3} and large inhaled doses from a metre-dosed inhaler.^{4 5}

Since the late 1990s, it has been accepted that adrenergic stimulation of gluconeogenesis, glycogenolysis and glycolysis causes an increased production of lactate, resulting in lactic acidosis.⁵ This is not unique to asthma exacerbations and has been reported in acute exacerbations of chronic obstructive pulmonary disease.²

Figure 1 summarises the physiological response to salbutamol therapy and how this was misinterpreted. The patient took a high frequency of inhaled salbutamol from a metre-dosed inhaler at home and had nebulised treatment before his first ABG, resulting in the high initial value (table 1). He was clinically stable, without signs of sepsis, making type A lactataemia unlikely. His repeat gases at 4 and 5.5 h showed a significantly improved A-a gradient, likely due to an improvement in his asthma. His persistently elevated respiratory rate was compensation for the lactataemia. It is at this point that peak flow measurements are crucial. If, as expected, they showed improvement, it would make it very unlikely that the situation was caused by a worsening of his asthma. Peak flow assessment

remains a cornerstone of the assessment of asthma exacerbations.⁶ Instead, in this case, the decision was taken to escalate treatment (table 1), leading to further metabolic derangement, confusion over the diagnosis and potential harm to the patient (figure 1).

Increase in lactate secondary to inhaled β agonist therapy is more common than generally recognised. In a prospective study⁷ of 18 patients with acute exacerbation of asthma, attending the emergency department, the change in lactate levels after administering 1200 μ g of inhaled salbutamol over 120 min was assessed. Fifty per cent of patients had increased lactate levels of over 2.5 mmol/L, and were over 4 mmol/L in four of these. However, none of these patients had acidosis.

Patient's perspective

I was admitted with a severe asthma attack and was advised that I suffered a small heart attack. This aggravated my asthma problem but I have since learnt that this was a side effect of the nebuliser use.

Learning points

- ▶ Salbutamol-induced lactic acidosis should be considered in an asthma exacerbation:
 - if there are no signs of shock or hypoperfusion;
 - if the lactate rises rapidly after salbutamol therapy;
 - if the lactate level rise is associated with an objective improvement in hypoxaemia and peak flow (or forced expiratory volume in 1 s (FEV₁)).
- ▶ Treatment of salbutamol-induced lactic acidosis is to reduce the salbutamol frequency.
- ▶ Peak flow or FEV₁ measurement by a peak flow metre or a bedside spirometer is an essential bedside tool that should be used to monitor response to treatment in an asthma exacerbation.

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