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lesson of the month (2)

Treating acute asthma – salbutamol may not always be the right answer

β_2 agonists are used as first-line treatment in acute asthma. However, they may paradoxically worsen respiratory failure through development of lactic acidosis.

Lesson

A 48-year-old asthmatic woman presented to the emergency department with worsening breathlessness following a week's history of dry cough and wheeze. She had been started on amoxicillin by her GP, with no improvement in her symptoms.

The patient was a non-smoker with a history of asthma since childhood. She had never been seen by a respiratory physician. She moved house four months prior to admission, which coincided with deterioration in her asthma control. She had been using her salbutamol inhaler at least six times per day and was waking once or twice a night with symptoms of asthma. Her last hospital admission had been many years ago. Her baseline peak expiratory flow rate (PEFR) was 300 l/min.

On presentation to the emergency department, the patient was alert and afebrile, with oxygen saturation of 96% on air. Her respiratory rate was 40 breaths per minute (bpm), with bilateral wheeze on chest examination. Apart from a sinus tachycardia (104 beats per minute), there were no other abnormal cardiac findings. A diagnosis of acute severe asthma was made, and treatment with 40 mg oral prednisolone and nebulised 500 μg ipratropium bromide and 5 mg salbutamol was initiated by the team in the emergency department.

The patient was seen 5 hours later in the medical admissions unit, having received 25 mg of nebulised salbutamol. She remained dyspnoeic, tachypnoeic (40 bpm) and tachycardic. Repeat respiratory examination revealed minimal scattered wheeze and oxygen saturation of 97% on 8 l/m of inspired oxygen. An increased white cell count (17×10^9/l) with neutrophilia was noted. C-reactive protein, electrolytes and liver function were normal. An electrocardiogram revealed sinus tachycardia with no acute changes, and chest x-ray was normal. Significant lactic acidosis was seen when arterial blood gas (ABG) was measured on 8 l/m of inspired oxygen (pH 7.438, carbon dioxide partial pressure 3.35 kPa, oxygen partial pressure 15.15 kPa, base excess –5.9 mmol/l, hydrogen carbonate ion 16.6 mmol/l and lactate 6.2 mmol/l). The patient was given further treatment with 2 g intravenous magnesium, intravenous aminophylline, intravenous fluid, intravenous antibiotics and back-to-back nebulised salbutamol.

Repeat ABG showed worsening of lactic acidosis (lactate 8.7 mmol/l). The possibility of salbutamol-induced lactic acidosis with secondary hyperventilation was considered, as there was no other obvious cause for the high levels of lactate. At this stage, nebulised salbutamol was replaced with nebulised terbutaline, which led to only a slight improvement in the level of lactate (7.0 mmol/l). This was therefore stopped in case of a β_2-agonist class effect. All other medications were continued. Over the next 3.5 hours her tachypnoea settled, and there was a significant reduction in lactate levels (4.6 mmol/l) and improvement in other clinical signs (Fig 1). She continued to improve and was discharged after four days.

Discussion

This case describes worsening tachypnoea due to lactic acidosis in a patient presenting with acute severe asthma without significant hypoxia. The lactic acidosis was transient, in this case lasting less than 24 hours, and settled on discontinuation of inhaled β_2-agonist therapy. There was no evidence of cardiac, liver or gut ischaemia or overwhelming sepsis as a cause of her lactic acidosis, while the lactate level was higher than would have been expected due to increased respiratory muscle work alone.

Lactic acidosis has previously been seen in acute exacerbations of asthma and was attributed to a combination of increased respiratory muscle work and hypoxaemia.[1] It was often not felt to be significant, although there have now been cases linked to the use of β_2-agonist therapy, both intravenous and inhaled, that have lead to inappropriate escalation in bronchodilator therapy[2,3] or respiratory failure leading to intubation.[4] Lactic acidosis has also been seen in paralysed and ventilated patients in whom respiratory muscle work is minimised[5,6] and in patients treated with β_2 agonists during preterm labour.[7] The number of reported cases of lactic acidosis relating to inhaled β_2 agonists alone is low.

In this case, our patient only received inhaled β_2-agonist therapy, initially in the form of salbutamol and subsequently as terbutaline. There was no obvious alternative cause for her lactic acidosis and her lactate level returned to normal despite continuation of all other medications. There was minimal improvement following the conversion of salbutamol to terbutaline, which seems to indicate a class effect.

The exact mechanism underlying the development of hyperlacticaemia relating to β_2-agonist therapy is unclear. Various

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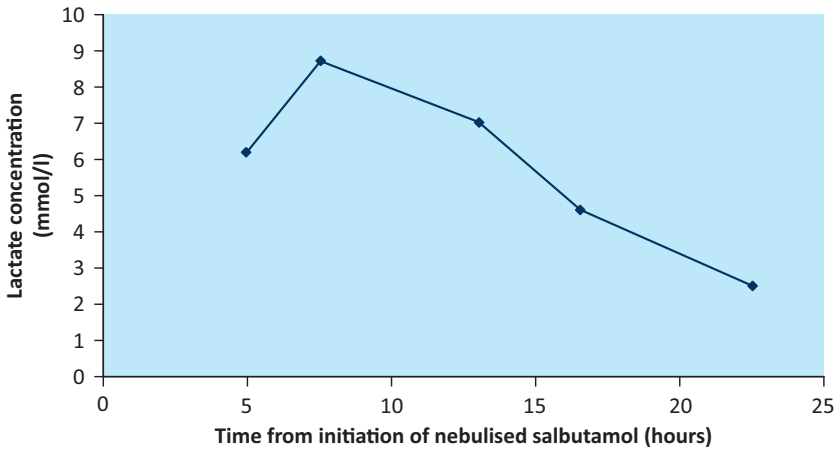

Fig 1. Change in concentration of lactate in serum over time.

metabolic pathways are affected by the stimulation of β-adrenoceptors, which results in increases in glycogenolysis,[8] gluconeogenesis and lipolysis. An increase in free fatty acids prevents the conversion of pyruvate to acetyl coenzyme A and therefore increases production of lactate.[5] Glucocorticoids and theophyllines have also been seen to enhance sensitivity of the β-adrenoceptors and therefore increase the likelihood of the events explained above.[6] Salbutamol, in both intravenous and nebulised forms, seems to cause a dose-dependent increase in basal metabolic rate and hence oxygen demand. As respiratory rate increases to compensate for this, hyperinflation worsens and respiratory mechanics are affected, which results in respiratory muscle failure.[8,9]

Conclusion

The first-line treatment of acute asthma is nebulised bronchodilator therapy and, in most cases, this will provide symptomatic relief of wheeze and breathlessness. This case highlights the need for repeated clinical assessment to ensure a good response to treatment. In cases of persistent tachypnoea, or discrepancy between PEFR and respiratory rate, hyperlacticaemia secondary to β_2-agonist therapy should be considered.

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