Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/mjafi

Case report

Metabolic acidosis due to inhaled salbutamol toxicity: A hazardous side effect complicating management of suspected cases of acute severe asthma

Lt Col R.P.S. Tomar^{a,*}, Col R. Vasudevan^b^aClassified Specialist, Dept of Paediatrics & Neonatology, MH Jalandhar Cant, Punjab 144005, India^bSenior Advisor, Dept of Paediatrics & Neonatology, MH Jalandhar Cant, Punjab 144005, India

ARTICLE INFO

Article history:

Received 22 May 2011

Received in revised form

14 September 2011

Accepted 8 October 2011

Available online 10 May 2012

Keywords:

Salbutamol toxicity

Metabolic acidosis

Acute asthma

ABSTRACT

Metabolic acidosis has seldom been reported during treatment of asthma with use of beta agonist but not with much clinical consequence. We report two cases of metabolic acidosis with hyperventilation as a direct effect of salbutamol that caused difficulty in assessment and management of their respiratory symptoms which resolved with appropriate tapering of beta agonist.

© 2012, Armed Forces Medical Services (AFMS). All rights reserved.

Introduction

Selective beta-2 agonists (salbutamol) have been the mainstay of acute asthma management since the late 1970s. Their early and aggressive use has decreased the number of children admitted to critical care units.¹ Most adverse effects of b-agonists in asthma are of cardiovascular nature such as tachycardia, increased QTc interval, dysrhythmia, hypertension or hypotension.² Other adverse effects of b-agonists include hypokalemia, tremor and worsening of ventilation/perfusion mismatch.¹ Metabolic acidosis has seldom been reported with severe exacerbation of asthma and has been hypothesized to result from lactic acidosis due inadequate oxygen delivery to the exerting respiratory muscles.³ But the development of this metabolic acidosis seen in children with

asthma may be related to use of inhaled salbutamol. We report two cases of metabolic acidosis with hyperventilation as a direct effect of salbutamol that caused difficulty in assessment and management of their respiratory symptoms. No common etiologies were found for this acidosis which resolved with appropriate tapering of beta agonist. We review the literature and discuss the mechanism by which lactic acidosis may occur in such patients.

Case 1

A 20-month-old male child was admitted with complaints of mild fever associated with cough for 3 days and progressive breathlessness for 1 day. Before admission he was treated

* Corresponding author. Tel.: +5533 (o), +9876671871 (mobile).

E-mail address: tomar15@rediffmail.com (R.P.S. Tomar).

0377-1237/\$ – see front matter © 2012, Armed Forces Medical Services (AFMS). All rights reserved.

doi:[10.1016/j.mjafi.2011.10.002](https://doi.org/10.1016/j.mjafi.2011.10.002)

with oral amoxicillin and syrup salbutamol and later intermittent salbutamol nebulization, which was progressively increased as his condition continued to deteriorate, when he was referred for admission. There was no history of previous wheezing, cyanosis, cough/choking spells suggestive of foreign body aspiration or family history of atopy or asthma. On admission the child was drowsy but arousable to touch, afebrile with respiratory rate 38 breaths/min, HR-166 beats/min, blood pressure 104/68 mm Hg, CFT < 3 s, SpO₂: 96% on 6 l/min of oxygen. Respiratory examination revealed mild suprasternal & subcostal recessions with inspiratory wheeze. Auscultation revealed bilateral ronchi. Other systems were normal. He received three doses of salbutamol nebulization combined with ipratropium bromide followed with frequent salbutamol nebulization, inj hydrocortisone along with injectable cefalosporins. Laboratory investigations revealed pH 7.28, PCO₂ 33 Torr, PO₂ 92 Torr, HCO₃ 15 mmol/L, anion gap 19 mmol/L, blood sugar of 218 mg/dl, no glycosuria or ketonuria with normal counts and a negative CRP. Chest radiograph was normal. Blood lactate could not be done. During next 2 h, he continued to be tachypenic with blood gas showing persistent acidosis despite clinical improvement. In view of no prior history of wheezing and no other apparent cause for persistent metabolic acidosis including hypoxia, hypovolemia or sepsis, a possibility of beta agonist toxicity was considered and salbutamol nebulization was stopped following which he showed rapid improvement with tachypnea disappearing within next 6 h, blood glucose declined to 138 mg/dl and blood gas normalized in next 24 h. He was subsequently discharged in a stable condition.

Case 2

An 8-year-old female child was admitted with complaints of progressive cough, chest discomfort and shortness of breath for past 1 week. She was diagnosed as asthma 2 months back for persistent cough and had been taking salmeterol/fluticasone by inhalation twice a day and salbutamol by inhalation once a day. 2 Days before presentation she had taken several back to back doses of salbutamol nebulization without relief. Her examination revealed temperature of 37 °C, respiratory rate 42 breaths/min, heart rate of 152/min, blood pressure 114/72 mm of Hg, capillary refill time < 3 s, SpO₂ of 92% on room air with difficulty in speaking and wheezing associated with mild chest retractions. She was treated with three doses of salbutamol combined with ipratropim bromide, hydrocortisone along with injectable amoxicillin/cluvanic acid. She continued to have tachypnoea with respiratory rate-51 breaths/min. Her blood showed pH of 7.23, PCO₂ 28 Torr, PO₂ 84 Torr, HCO₃ 12 mmol/L, anion gap of 18 mmol/L with blood glucose of 223 mg/dl. Blood lactate was 12.9 mmol/L. Her chest radiograph was normal. With an impression of clinical deterioration and impending respiratory failure she was give subcutaneous injection of terbutaline, magnesium sulfate intravenously and theophylline infusion. As all common causes of metabolic acidosis in her case were excluded, this lactic acidosis was suspected to be secondary to increased nebulized salbutamol which was consequently reduced to intermittent inhalation (6 h) while ipratropium and

theophylline were continued. During the next 8 h her condition gradually improved with decrease in dyspnoea, normalization of blood gases and blood glucose declining to 148 mg/dl. All her medications were gradually stopped subsequently and she was discharged on the sixth day.

Discussion

Salbutamol, a beta agonist is associated with side effects.^{1,2} One of the least recognized side effects of salbutamol treatment is metabolic acidosis due to development of lactic acidosis.^{3,4} It had been previously reported with intravenous beta agonist therapy used to prevent preterm labour⁵ or salbutamol overdose.⁶ Till now there were isolated case reports in children describing beta agonist induced lactic acidosis,⁷ but in a significant study, metabolic acidosis with hyperventilation was seen in 28% of the 53 children treated with beta agonist for acute asthma.⁸ This was also reported by Dr Ramnarayan et al from the UK Children's Acute Transport Service.⁹

In general, metabolic acidosis due lactic acidosis is commonly associated with increased production with decreased tissue perfusion either due to hypoperfusion, hypoxia or sepsis. It could also be undermetabolized by a hypoxic liver. Increased production of lactic acidosis in respiratory distress such as in asthma has been proposed to result from overuse of respiratory muscles under hypoxic conditions.³ However, increased lactic acidosis has been found to occur even in those patients whose work of breathing is minimized by mechanical ventilation and pharmacological paralysis.⁴ Other proposed causes of lactic acidosis are reduced cardiac output due to elevated intrathoracic pressures or hypovolemia. Hypovolemia may be significant in children with respiratory distress due to decreased intake, increased insensible losses and hyperglycemia due to beta agonist and glucocorticoids.⁷ This hyperglycemia may cause glucosuria, osmotic diuresis, decreased tissue perfusion and increased potential for lactic acidosis. Regardless of the etiology of lactic acidosis, beta agonist therapy may exacerbate its magnitude. Both of these children had no evidence of renal or hepatic dysfunction. Neither there was any evidence of hypoperfusion or hypotension as their urine output was normal with normal mean pressures nor did they have any evidence of end organ dysfunction typical of shock.

The mechanisms by which beta agonists produce lactic acidosis remain uncertain. It has been hypothesized that beta adrenergic receptor stimulation causes enhanced cyclic adenosine monophosphate (cAMP) mediated gluconeogenesis and lipolysis. This increased plasma glucose concentration is converted to pyruvate via glycolysis which is then converted to lactate. Skeletal muscle glycogenolysis is a major source of this lactate production since they lack glucose-6-phosphatase. Therefore glucose-6-phosphate is converted to pyruvate via glycolysis (Fig. 1). Simultaneously the free fatty acids released by lipolysis inhibit the oxidation of pyruvate to acetyl-coenzyme A, thereby providing increased substrate for lactate formation.^{8,10} Finally, a number of other agents used to treat asthma, such as glucocorticoids and theophylline, may potentiate the metabolic effects of beta adrenergic agonists by

Fig. 1 – Biochemical pathways by which beta 2-agonists lead to increased lactate production.

increasing intracellular levels of cAMP and further amplifying the above described events.¹⁰

Thus development of lactic acid induced metabolic acidosis causes hyperventilation which should be recognized as a compensatory mechanism to maintain body pH and not mistaken as sign of worsening respiratory condition. Cases have been reported of inappropriate escalation of beta agonist therapy in dyspnoea associated with metabolic acidosis.¹¹ In these cases, metabolic acidosis resolved after tapering of beta agonist, similar to our cases. Although it is sometimes difficult to establish a cause-effect relationship with resolving metabolic acidosis and decreasing beta agonist therapy due to which it is either not recognized or has been under-reported. In some patients the metabolic acidosis may be masked by superimposed respiratory alkalosis which is seen early in the attack when patients are frequently hypocarbic. Also many such patients receive supplemental bicarbonate therapy. Meert et al reported a very high incidence of metabolic acidosis due to beta agonist in 28% of the 53 children over 1 year.⁸ This magnitude had not been reported in previous series.⁷ The difference that not all patients treated with beta agonist develop acidosis could probably be due to intersubject variability in genetic polymorphisms in beta agonist receptors¹² as well as dose and duration of therapy. Metabolic derangement effects of salbutamol were more related to higher doses, longer duration of exposure and more observed with intravenous infusions.

In summary the potential for beta agonist toxicity should be recognized in a wheezing, restless, tachycardic and hyperglycemic child who has been on escalating doses of inhaled salbutamol and with blood gas analysis showing metabolic acidosis and hypocapnia (with $\text{PCO}_2 < 35$ Torr the severity of airway obstruction has quite likely decreased

sufficiently to reduce beta 2 agonist therapy). It should alert the physician for an urgent need for change in therapy so as to resolve the symptoms. Ketonuria may act as an early marker of salbutamol toxicity.⁹ The physician who decides to escalate therapy based only on the amount of wheezing may make his patient worse. Caution must always be taken in drawing conclusions in relationship with persistent or worsening of respiratory distress due metabolic acidosis and hyperventilation in children treated with beta agonist since adverse effects do not differ from the symptoms caused by asthma itself. It is important to undertake the tapering strategy in a secure intensive environment with the use of ABG analysis, while looking at the alveolo-arterial oxygen gradient, to find the right direction of management. In the first case we could immediately stop the salbutamol while the second case was sicker and hence we continued ipratropium as a reliever therapy for any anticipated deterioration.

Conflicts of interest

None identified.

REFERENCES

1. Robinson PD, Van Asperen P. Asthma in childhood. *Pediatr Clin N Am*. 2009;56:191–226.
2. Maguire JF, O'Rourke P, Colan SD, et al. Cardiotoxicity during treatment of severe childhood asthma. *Pediatrics*. 1991;88:1180–1186.
3. Manthous CA. Lactic acidosis in status asthmaticus: Three cases and review of the literature. *Chest*. 2001;19:1599–1602.
4. Rodrigo GJ, Rodrigo C. Elevated plasma lactate level associated with high dose inhaled albuterol therapy in acute severe asthma. *Emerg Med J*. 2005;22:404–408.
5. Cotton DB, Strassner HT, Lipson LG, et al. The effects of terbutaline on acid base, serum electrolytes, and glucose homeostasis during the management of preterm labor. *Am J Obstet Gynecol*. 1981;141:617–624.
6. Habib GS, Saliba WR, Cohen L. Diabetic ketoacidosis associated with oral salbutamol overdose. *Am J Med*. 2002;113:701–702.
7. Yousef E, McGeady SJ. Lactic acidosis and status asthmaticus: how common in pediatrics? *Ann Allergy Asthma Immunol*. 2002;89:585–588.
8. Meert KL, Clark J, Sarnaik AP. Metabolic acidosis as an underlying mechanism of respiratory distress in children with severe acute asthma. *Pediatr Crit Care Med*. 2007;8:519–523.
9. Ramnarayan P, Chhabra R, Maheshwari P. Metabolic acidosis, respiratory distress, and children with severe acute asthma. *Pediatr Crit Care Med*. 2009;10:142.
10. Olson MS. Bioenergetics and Oxidative Metabolism. In: Devlin TM, ed. *Textbook of Biochemistry with Clinical Correlations*. 3rd ed. New York: Wiley-Liss; 1992:237–289.
11. Prakash S, Mehta S. Lactic acidosis in asthma: report of two cases and review of literature. *Can Respir J*. 2002;9:203–208.
12. Bhatnagar P, Guleria R, Kukreti R. Pharmacogenomics of beta 2-agonist: Key focus on signaling pathways. *Pharmacogenomics*. 2006;7:919–919.