



Case report

Lactic acidosis and diastolic hypotension after intermittent albuterol nebulization in a pediatric patient



Tehila A. Saadia, Mathew George*, Haesoon Lee

Division of Pediatric Pulmonology, Department of Pediatrics, SUNY Downstate Medical Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA

ARTICLE INFO

Article history:

Received 28 July 2015

Accepted 12 August 2015

Keywords:

Albuterol
 β_2 -agonist
 Diastolic hypotension
 Lactic acidosis
 Asthma

ABSTRACT

We describe a case of 13-year-old female with intermittent asthma who developed lactic acidosis and diastolic hypotension after receiving intermittent albuterol nebulizer treatment. She presented to the emergency department (ED) with sudden onset of shortness of breath and chest pain. She received two albuterol nebulizer treatments at home without symptomatic relief. She was treated in the ED with intermittent albuterol nebulization for a total of 22.5 mg over the next 5 hours. A decrease in diastolic blood pressure from 60 mmHg to 40 mmHg was noted after the treatment. Blood lactate level was 5.9 mmol/L. She recovered from it and was discharged to home but she had recurrence of shortness of breath and presented to the ED two days later. She was treated with albuterol nebulization for a total of 17.5 mg over the next two and half hours and developed diastolic hypotension again, as low as 30 mm Hg. After discontinuation of albuterol nebulization, her BP normalized. Cardiopulmonary and metabolic side effects of continuous albuterol therapy have been reported in the recent medical literature. Our patient, however, developed these adverse effects on intermittent albuterol nebulizer treatment. It is important for the pediatrician to recognize the adverse effects of β_2 -agonist therapy to avoid carrying out extensive workup for hypotension and hyperlactatemia prolonging hospital stay.

© 2015 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Nebulized albuterol is used widely for asthma patients during asthma exacerbation and it is deemed safe for both intermittent and continuous administration. Cardiopulmonary and metabolic side effects have been noted with continuous albuterol therapy in the recent medical literature. In pediatric patients in the emergency department or hospitalized, these side effects can be more pronounced with repeated dosing of albuterol. It is important for the pediatricians to recognize the side effects of β_2 -agonist therapy in order to manage the patients appropriately. We report a case of a 13-year-old girl with asthma, who required Pediatric Intensive Care Unit (PICU) admission for low diastolic blood pressure refractory to fluid therapy after receiving intermittent β_2 -agonist nebulization.

2. Case presentation

A 13-year-old female with intermittent asthma presented to the emergency department (ED) with sudden onset of shortness of

breath and chest pain.

She received two albuterol nebulizer treatments at home without symptomatic relief before coming to the ED. Her vital signs were respiratory rate (RR) of 28–36/min, blood pressure (BP) of 99/60 mm Hg (within normal range for her age and height of 160 cm), temperature of 99.8 F, pulse of 88/min, and oxygen saturation of 99% on room air. No wheezing was heard on auscultation. In light of the tachypnea and history of asthma, she was treated for acute asthma exacerbation with repeated intermittent nebulized albuterol, 22.5 mg in 5 h, and dexamethasone 10 mg intravenously (IV). She reported slight improvement in her symptoms. Her repeat BP was 90/40 mm Hg after receiving 22.5 mg of nebulized albuterol over 5 hours in the ED. She was administered one liter of normal saline (NS) bolus. Arterial blood gas revealed pH of 7.22, $p\text{CO}_2$ of 40.9 mm Hg, $p\text{O}_2$ of 52.3 mm Hg, oxygen saturation of 80.3%, HCO_3 of 16.2 mEq/L, base excess of -9.7 , and lactate level of 5.9 mmol/L (normal range 0.5–2.2). Basic metabolic panel (BMP) revealed Na 142 mmol/L, K 3.2 mmol/L, Cl 106 mmol/L, CO_2 15 mmol/L, BUN 14 mg/dl, and creatinine 0.72 mg/dl, with an anion gap of 21. Patient was admitted to the pediatric ward ten hours after initial presentation with BP of 103/44 mm Hg. Nebulized albuterol 2.5 mg was continued every two hours for two more doses. 14 h after initial

* Corresponding author.

E-mail address: Mathew.george@downstate.edu (M. George).

presentation, patient complained of dizziness coinciding with BP of 72/44 mm Hg and a pulse of 120 beats per minute (normal for age is 48–110). Patient was then administered a second one liter bolus of NS and was transferred to the Pediatric Intensive Care Unit (PICU). In the PICU, she received another one liter bolus of NS and was started on continuous nebulization of albuterol 5 mg/h for one hour. She was then noted to be free of wheezing and her symptoms were thought to be related to panic attack. Albuterol was discontinued and IV fluids were continued at her maintenance rate. Within one hour of discontinuation of nebulized albuterol, her BP normalized at 103/59 mm Hg and her dizziness resolved. It was thought that her shortness of breath was most likely secondary to anxiety. Her electrocardiogram and echocardiogram were normal and repeat lactate was 2.9 mmol/L before she was discharged to home the following day.

She felt fine for the next two days after discharge, and then she suddenly started to complain of chest tightness and non-radiating midsternal chest pain of 8/10 intensity, associated with tachypnea and a feeling of “not getting any air into my lungs” that was aggravated by deep breathing. In the ED, her vital signs were RR of 26–30/min, pulse of 100/min, BP of 128/78 mm Hg, temperature of 99 F, and oxygen saturation of 98% on room air. She was treated for status asthmaticus with intermittent nebulized albuterol 17.5 mg over the next two and half hours, IV magnesium sulfate 2 g along with one liter bolus of NS, and IV solumedrol 60 mg. She was admitted to the pediatric ward and was treated with nebulized albuterol every two hours for three times. Her BP was 90/30 mm Hg on arrival at the pediatric ward, and it was 108/37, 98/43, 99/43, 90/34 and 78/32 mm Hg in the next 3 h. Her BP failed to respond to two additional one liter boluses of NS, and she was transferred to the PICU. In the PICU, she was free of wheezing and nebulized albuterol was discontinued. Her BP was 96/50 mm Hg 90 min after discontinuation of nebulized albuterol. In the next 24 h, her BP normalized and she was transferred back to the ward, where her BP remained above 90/50 mmHg for the remainder of her hospital stay. She was discharged to home after 24 h of observation without IV fluids. Lactic acid level was not determined during the second admission.

3. Discussion

Albuterol is a direct acting sympathomimetic agent used for its bronchodilator effect on β_2 -receptors of the lungs [1]. Mild tachycardia is common when patients are treated with β_2 -agonist. Other cardiovascular adverse effects of β -agonists are QT interval prolongation in the electrocardiogram, hypertension, and rarely, cardiac ischemia and arrhythmias [2]. The mechanism of hypotension after beta agonist therapy is thought to be secondary to its effect on systemic vascular resistance and peripheral vasodilation [3]. Tachycardia may result from dilation of peripheral vasculature that reduces venous return, which results in sympathetic nervous system reflexes and increased inotropic and chronotropic effects [2]. Sarnaik et al. demonstrated that diastolic hypotension occurred in 56% of children transported to the hospital for respiratory distress who received at least 10 mg of nebulized albuterol per hour and 98% of children with diagnosis of status asthmaticus who had received at least 10 mg of nebulized albuterol per hour and had measurement of troponin level. Diastolic hypotension and tachycardia were associated with elevated troponin levels, indicative of possible myocardial injury [4]. A similar study by Wisecup et al., illustrated a dose-dependent diastolic hypotension on continuous albuterol nebulization therapy in 90% of patients admitted to pediatric intensive or intermediate care units for management of status asthmaticus [4]. The combination of tachycardia and diastolic hypotension can be detrimental to myocardial perfusion.

With tachycardia, shortening of diastolic duration can decrease the blood perfusion to the sub-endocardium [5,6]. With increased myocardial oxygen demand coupled with decreased coronary perfusion pressure and decreased diastolic time fraction may result in decreased myocardial oxygen supply to meet the demand.

Lactic acidosis is a well-established phenomenon in patients with severe asthma and has been hypothesized, by some, to result from inadequate oxygen delivery to the respiratory muscles, the diaphragm, to meet an elevated oxygen demand [7]. During a severe asthma attack, hypoxemia alone may lead to what is known as “type A” lactic acidosis, which can occur in poor tissue perfusion, shock, or hypoxia. On the other hand, “type B” lactic acidosis occurs from decreased lactate metabolism in the absence of tissue hypoperfusion. Type A and B lactic acidosis can be distinguished by the ratio of lactate to pyruvate concentrations in the blood [7]. In type A the ratio is usually above 25:1. In a PICU study by Meerk et al. of the 105 pediatric asthma patients who received frequent or continuous albuterol nebulizations, eighty-seven (83%) children had lactate >2.2 mmol/L and 47 (45%) had lactate >5 mmol/L. Lactate/pyruvate ratios were determined in 16 patients. Lactate/pyruvate ratio was <10 in three patients; 10–25 in 11; >25 in one and indeterminate in one patient. They concluded that type B lactic acidosis was more common in patients receiving frequent albuterol nebulization [7]. Another retrospective study also showed similarly high number of patients developing elevated lactic acid after beta agonist inhalation or IV therapy for asthma. Of 75 pediatric patients who had asthma exacerbation and were treated with nebulized or intravenous albuterol, 55 patients had lactate level measured; 39 patients (71%) had lactic acidosis with lactate level >2.2 mmol/L, and 12 (22%) had lactate level >5 mmol/L [8].

The mechanisms by which beta-agonists may cause lactic acidemia are many. Stimulation of β -adrenoreceptors increases plasma glucose concentrations, thus increasing substrate for glycolysis. The end product of glycolysis, pyruvate can then diffuse into the mitochondria and metabolized to carbon dioxide by another, more energy-efficient metabolic pathway, the Krebs cycle. If the pathway is overwhelmed, the excess pyruvate is converted to lactic acid by pyruvate dehydrogenase complex. Stimulation of β adrenoreceptors also increases lipolysis and β_2 stimulation appears to increase lipolysis to a greater degree than β_1 stimulation. Increased free fatty acids inhibit conversion of pyruvate to acetyl-coenzyme A with consequent increases in lactic acid. Thus, a number of mechanisms may play role in lactic acidemia in patients with asthma receiving nebulized or IV β_2 -agonists, usually in high doses. Finally, glucocorticoids and sometimes theophylline used concomitantly with beta-agonist inhalants in patients with obstructive airways disease increase the level of intracellular cAMP and may enhance the sensitivity of β -receptors to β -adrenergic agents that may further amplify the above described event [9]. As our patient did not receive high dose of continuous albuterol nebulization as part of her ED management of asthma (calculated as approximately 4.5 mg/h for 5 h in the ED during the initial hospitalization and 7 mg/h for two and half hours in the ED during the second hospitalization), the cause of her diastolic hypotension is not obvious. This could be due to the peripheral vasodilation impeding venous return to heart causing diastolic hypotension.

There may have been other causes of hypotension in our patient, such as postural orthostatic hypotension, relative dehydration, or due to magnesium sulfate she received in the ED on second admission; however, the prolonged hypotension does not explain the magnesium sulfate induced hypotension. Her hydration status was adequate. According to Naranjo’s Adverse Drug Reaction (ADR) scale for this case, the score was 6, indicating probable cause of adverse reaction to albuterol (>9 = definite ADR, 5–8 = probable ADR, 1–4 = possible ADR 0 = doubtful ADR) [10]. The rapid reversal

of hypotension and lactic acidosis after discontinuation of albuterol is suggestive of the albuterol as the culprit for both lactic acidosis and hypotension. It is also important to recognize that in the asthmatic patient treated with albuterol, the acidotic state may worsen tachypnea and mislead the physician to increase albuterol treatments, contributing to worsening of cardiovascular adverse events and lactic acidosis.

Acknowledgments

None.

References

- [1] M. Johnson, The beta adreno receptor, *Am. J. Respir. Crit. Care Med.* 158 (1998) s146–156.
- [2] M.R. Sears, Adverse effects of beta-agonists, *J. Allergy Clin. Immunol.* 10 (Suppl. 6) (2002) S322–S328.
- [3] E.M. Snyder, E.C. Wong, W.T. Foxx-Lupo, C.M. Wheatley, N.A. Cassuto, A.E. Patanwala, Effects of an inhaled β_2 -agonist on cardiovascular function and sympathetic activity in healthy subjects, *Pharmacotherapy* 31 (8) (2011) 748–756.
- [4] S.M. Sarnaik, R.A. Saladino, M. Manole, R.A. Pitetti, G. Arora, B.A. Kuch, R.A. Orr, K.A. Felmet, Diastolic hypotension is an unrecognized risk factor for β -agonist-associated myocardial injury in children with asthma, *Pediatr. Crit. Care Med.* 14 (6) (2013) e273–e279.
- [5] S. Wisecup, S. Eades, S.S. Hashmi, C. Samuels, R.A. Mosquera, Diastolic hypotension in pediatric patients with asthma receiving continuous albuterol, *J. Asthma* 4 (2015) 1–6.
- [6] T.W. Hein, C. Zhang, W. Wang, L. Kuo, Heterogeneous beta2-adrenoceptor expression and dilation in coronary arterioles across the left ventricular wall, *Circulation* 110 (17) (2004; 26) 2708–2712.
- [7] K.L. Meert, L. McCaulley, A.P. Sarnaik, Mechanism of lactic acidosis in children with acute severe asthma, *Pediatr. Crit. Care Med.* 13 (1) (2012) 28–31.
- [8] S.A. Walsh, R.I. Paget, P. Ramnarayan, Salbutamol usage and lactic acidosis in acute severe asthma, *Pediatr. Crit. Care Med.* 14 (1) (2013) 116–117.
- [9] M. Reverte, M.J. Garcia-Barrado, J. Moratinos, Changes in plasma glucose and lactate evoked by α - and β_2 -adrenoceptor stimulation in conscious fasted rabbits, *Fundam. Clin. Pharmacol.* 5 (1991) 663–676.
- [10] C.A. Naranjo, U. Busto, E.M. Sellers, et al., A method for estimating the probability of adverse drug reactions, *Clin. Pharmacol. Ther.* 30 (1981) 239–245.