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Case Report

Minimal dose inhaled salbutamol leading to diastolic hypotension (rare presentation) and significant lactic acidosis mimicking shock, a case report from tertiary care hospital in Ajman, UAE

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ABSTRACT

Salbutamol is a selective β2-receptor agonist widely used to treat asthma in both emergency and outpatient settings. It has been associated with a various side effects ranging from mild to severe in presentation. Lactic acidosis and diastolic hypotension are rarely reported together following intermittent salbutamol nebulization in children, even less so at standard therapeutic doses. We present the case of an 11-year-old Emirati male child, known asthmatic but not on any preventive therapy, who experienced a serious drug reaction during an asthma exacerbation following inhaled salbutamol (5 mg back to back, overall 5 to 10 mg. while he was receiving the second dose of salbutamol nebulization in our emergency department, he developed persistent hypotension (lowest 70/45) despite fluid boluses, also he had elevated blood lactate levels (peak concentration 9 mmol/l), following the hyperglycemia (peak concentration 18 mmol/l), hypokalemia (lowest concentration 3.3 mEq/l).The aforementioned alterations improved within 24 hours after discontinuation of salbutamol and without any further fluid boluses which has been initiated initially at the causality based on the presentation that was mimicking shock status. We reinforce the message that even the use of intermittent nebulized salbutamol for acute moderate asthma can lead to severe transient complications in children. Then, healthcare providers should pay attention not only in emergency settings, to achieve prompt recognition and proper management of this adverse reaction. Careful reassessment could prevent similar reactions and further serious complications.

Keywords: Asthma exacerbations, Salbutamol adverse drug reaction, Lactic acidosis, Diastolic hypotension

INTRODUCTION

Bronchial asthma exacerbation is a leading cause of pediatric emergency department (PED) visits and hospital admissions. Salbutamol is widely regarded as the first-line treatment for managing asthma exacerbations.[1]

Both metered-dose inhalers with spacers and nebulizers are options for delivering bronchodilator therapy. The former is typically preferred for home use or milder exacerbations, while the latter is favored for managing more severe exacerbations, particularly in hypoxic and/or noncompliant patients in emergency situations. However, there has been an increase in reports of adverse cardiovascular and metabolic reactions to salbutamol.

It is crucial for pediatricians to quickly recognize these side effects to prevent negative outcomes and avoid inappropriate treatment. Herein we describe a serious drug reaction to a standard dose of intermittent nebulized salbutamol in an 11-year-old boy, who required admission to our PICU.

Objective

To present a rare case of minimal dose inhaled salbutamol leading to diastolic hypotension and significant lactic acidosis mimicking anaphylactic shock.

CASE REPORT

We present a case of 11 years old known asthmatic, not on any medication presented to our hospital Sheikh Khalifa Medical City, Ajman, UAE after consuming outside food (Noodles, KFC chicken, grape leaves), following which the child developed cold, shivering, vomiting, chest tightness, cough, and breathing difficulty. Symptoms progressively worsened, leading to drowsiness and weakness, prompting a visit to the hospital.

Vitals & measurements

Temperature: 37°C (tympanic), heart rate: 119 bpm (peripheral), respiratory rate: 36 Bpm, blood pressure: 101/62 (mmHg initial before salbutamol nebs, oxygen saturation: 99% in room air, capillary refill time: <2 seconds (normal)

General examination

Consciousness: alert and oriented, GCS 15/15. Chest: reduced air entry on the right side, faint wheezing. Heart: normal rate, rhythm, no murmurs or gallop. Abdomen: soft, non-tender, non-distended, normal bowel sounds. Skin: warm, dry, and pink with no rashes, normal capillary refill.

In view of respiratory distress bilateral wheeze and reduced air entry patient was advised salbutamol nebulization back to back 5 mg each in our urgent care, while patient was receiving the second dose of nebulization (total dose between 5-10 mg) the patient started to have low blood pressure predominantly diastolic hypotension reading in next 6 hours 104/55, 95/45, 99/46,94/36, 101/46, 106/44, 102, 47 but his capillary refill was normal, 2 sec and peripheries were warm and good volume peripheral pulses .Initial 20 mL/kg saline bolus given, followed by a second and third bolus of 20 ml/kg, totaling 60 ml/kg. However, blood pressure remained low, particularly the diastolic (45-50 mmHg). Patient has had history of similar reactions and the clinical course (wheezing, hypotension, as per parents post nebulization one year back and was managed with fluids and epinephrine as anaphylaxis was suspected at that time, in view of the background history, patient received an epinephrine IM dose of 0.5 mg, BP improved temporarily, but it dropped again. A second dose of epinephrine (0.5 mg IM) was given in the ED. But the clinical picture was less suggestive of anaphylaxis as there was no skin manifestations cap refill was good. Then, in view of persistent low blood pressure patient was admitted to PICU and norepinephrine infusion started through a peripheral line. Basic laboratory was done which was suggestive of blood gas: normal pH and bicarbonate; lactate 9 after 6 hours of fluid management after initial value of 2.9, WBC count of 10 (50% neutrophils), procalcitonin 0.08, CRP 9 and patient clinically not looking septic making septic shock a less possibility. Blood sugar was 18 mmol/l potassium level was 3.3. The patient's symptoms, particularly lactic acidosis, hyperglycemia (18 mmol/l), and decreasing potassium levels, raised concerns for an adverse reaction to salbutamol nebulization was immediately advised to discontinue and additional monitoring for tremors, hypokalemia, and further hyperglycemia was advised. Cardiac evaluation showed normal ECG, normal cardiac enzymes and normal ECHO cardiograph.

Nor epinephrine was continued at a low dose of 0.05 mcg/kg/min to support vascular resistance. Pulmicort (Budesonide) and ipratropium bromide nebulization were added for asthma management. And IV Fluids, adjusted for maintenance and hydration needs, with no further saline boluses required and nor-epinephrine was tapered off, as the patient's blood pressure started improving lactate was tracked closely and it started at 9, but after cessation of salbutamol, it dropped to 2.9 after around 6 hours. Glucose initially elevated at 18 mmol/l, but improved to 8 mmol/l after 8-10 hours of fluid management. Potassium corrected after initial depletion. Within 24 hours of fluid management and with holding the salbutamol patients' blood pressure normalized and lactate and hyperglycemia got corrected. Full counseling with the parents was done on the possible adverse effects of salbutamol and alternative asthma management strategies.

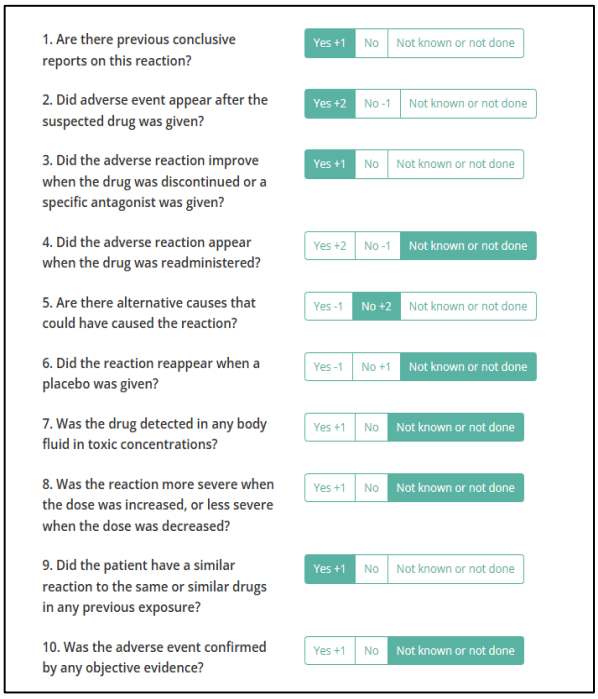

Figure 1: Naranjo's ADR correlation scale.[18]

DISCUSSION

Our case report highlights a severe adverse drug reaction (ADR) resulting from a minimal inhaled dose of salbutamol. While the use of spacers with metered-dose inhalers has been shown to be as effective as nebulization in treating asthma exacerbations.[1] Reports of adverse drug reactions have been rising in recent times. Mild tachycardia is a common occurrence when patients are treated with β2-agonists. Other cardiovascular side effects of β-agonists include QT interval prolongation on the electrocardiogram, hypertension, and, in rare cases, cardiac ischemia and arrhythmias.[2] According to Leung et al, although adverse drug reactions (ADRs) are reported in 34.6–52% of intermittent salbutamol administrations in children, only 6% of these are considered to be true ADRs.[3]

Although salbutamol is well-known for its selective action on β2 airway receptors, it also exhibits β1 activity, particularly at higher doses, as well as β3 activity, which contribute to its wide range of side effects.[4-6] Common side effects include tremor, dizziness, headache, reduced diastolic blood pressure (DBP), elevated troponin levels in the serum, hypokalemia, acute urinary retention, and lactic acidosis.[7-11] These effects result from β2-adrenergic receptor stimulation, which induces aerobic glycolysis, leading to hyperglycemia and an increased concentration of pyruvate in tissues. This pyruvate is then converted to lactate-by-lactate dehydrogenase, causing type B2 lactic acidosis. Diastolic hypotension results from the relaxation of vascular smooth muscle, which may reduce myocardial blood flow.[12]

This was first reported by Shurman et al, in 1984 in a 33-year-old man following salbutamol inhalation.[13] Severe side effects are more frequently observed after intravenous or oral administration, or when high-dose continuous nebulized therapy is used.[14] A study by Wisecup et al. demonstrated a dose-dependent diastolic hypotension in 90% of patients receiving continuous albuterol nebulization therapy, who were admitted to pediatric intensive or intermediate care units for the management of status asthmaticus. Additionally, corticosteroids may increase the sensitivity of β-adrenoceptors to sympathetic agents, thereby raising the risk of adverse drug reactions (ADR).[15]

Sarnaik et al, showed a dose-dependent effect of high-dose continuous inhaled salbutamol on diastolic blood pressure (DBP) in two groups of children with status asthmaticus during transport to the hospital or upon admission to the PICU. In these groups, 56% and 98% of children experienced at least one episode of low DBP, respectively.[8] Carrol et al, observed lower diastolic blood pressure (DBP) in 66% of children who received continuous salbutamol at a dose of 10–15 mg per hour for more than 2 hours.

Additionally, 15% of the patients showed ECG ST-segment changes, and 24% had elevated troponin-T serum levels. Furthermore, Wisecup et al, found that 90% of children receiving a median weight-based dose of 12.7 mg/kg of continuous nebulized salbutamol for status asthmaticus developed lower DBP, with a positive correlation to increasing doses severe adverse drug reactions (ADR) following intermittent nebulization are rarely reported in younger children, possibly due to less effective nebulizer techniques that result in lower drug absorption.[9]

In 2015, Saadia et al, reported the case of a 13-year-old female with intermittent asthma who developed lactic acidosis and diastolic hypotension after receiving 22.5 mg of salbutamol via intermittent nebulizer treatment.[16] These symptoms resolved after discontinuing the drug and recurred upon re-administration. Lactic acidosis is commonly observed in cases of poor tissue perfusion or asthma, possibly due to insufficient oxygen delivery to the respiratory muscles (type A lactic acidosis) and increased insensible loss caused by tachypnea.[17] In our patient, these factors might have generated lactic acidosis, whereas salbutamol treatment might have been a contributory aggravating factor. Interestingly, our patient experienced also hyperglycemia, and hypokalemia despite a lower dose than the ones reported in the citations. The diagnosis of salbutamol adverse drug reaction was high possibility in our patient with presence of hypokalemia, hyperglycemia, lactic acidosis and persistent diastolic hypotension.

There may have been other causes of hypotension, such as postural orthostatic hypotension, relative dehydration, or due to magnesium sulfate however patient was hydrated well no magnesium sulfate was used and even blood pressure did not improve immediately after making patient in a supine position. Finally, we applied the "Naranjo's ADR correlation scale, obtaining a score of 7, meaning "probable correlation" (>9 definite ADR, 5–8 probable ADR, 1–4 possible ADR, 0 doubtful ADR). Additionally, we ruled out other possible causes, including liver dysfunction, cardiac causes or sepsis.

We considered these findings as an early ADR following salbutamol nebulization rather than a delayed ADR following medications prior to arrival, for a few reasons: first, most of the side effects of short-acting β2 agonist show tolerance with chronic and repeated use, "Secondly, the patient did not report tremors upon admission, and both potassium and glucose serum levels, as well as blood pressure, were normal.[2] Although a recent large meta-analysis on lactic acidosis induced by selective β2-adrenoceptor agonists suggests that lactic acidosis is reversible even in patients who continue the medication withholding salbutamol, using an equally effective alternate drug to treat underlying conditions may be pivotal if it does not affect the acute care of the patient.[19]

In our patient, we decided to withdraw salbutamol reported by Seay et al, in a 14-year-old female who experienced severe lactic acidosis after intermittent and continuous salbutamol treatment.[20] Given this, the management of this kind of ADR is purely symptomatic. Hypokalemia should be corrected carefully with frequent assessment of potassium serum levels.

It has been suggested that administration of fluid boluses, before continuous nebulized salbutamol, might prevent diastolic hypotension however, to the best of our knowledge, evidence of the efficacy of such strategy before intermittent nebulized salbutamol is lacking in children.

CONCLUSION

In conclusion, to the best of our knowledge, we described a severe adverse drug reaction after the lowest dosage ever reported of intermittent nebulized salbutamol in a child presenting with moderate asthma exacerbation. Careful reassessment is desirable following each nebulization, clinicians should pay attention to otherwise unexplained lactic acidosis and/or persistent lower diastolic blood pressure while treating asthma exacerbations in children, even at standard doses of intermittent nebulized salbutamol, to prevent poor outcome and inappropriate management.

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