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Review Article

Diagnosis, complication and treatment of acute salbutamol toxicity

Maryam Abdullah Baik[1]*, Hassan Mohammed Alessa[2], Amnah Hassan Mohammed[3], Ibtihal Faisal Al Eid[4], Hanan Abdullah Almowallad[5], Yaqoub Yousef Alkhallafi[6], Somayya Khalid Khan[7], Ziad Abdulmoti Alruwaithi[8], Osamah Ali Albader[9], Abdulaziz Salah Al-Din Mahfouz[10], Fatemah Abdul Ameer Alshammaa[11]

[1]Department of Emergency Medicine, East Jeddah Hospital, Jeddah, Saudi Arabia
[2]Department of General Surgery, Al-Ahsa Health Cluster, Al Ahsa, Saudi Arabia
[3]College of Medicine, Jazan University, Jazan, Saudi Arabia
[4]Department of Emergency Medicine, Jubail General Hospital, Jubail, Saudi Arabia
[5]Department of Emergency Medicine, King Abdulaziz Hospital, Mecca, Saudi Arabia
[6]College of Medicine, Medical University of Lodz, Lodz, Poland
[7]College of Medicine, Umm Al-Qura University, Mecca, Saudi Arabia
[8]Emergency Medical Service, Ajyad Emergency Hospital, Mecca, Saudi Arabia
[9]Department of Emergency Medicine, Buraidah Central Hospital, Buraidah, Saudi Arabia
[10]General Physician, King Faisal Medical Complex, Taif, Saudi Arabia
[11]Department of Emergency Medicine, Al-Amiri Hospital, Kuwait City, Kuwait

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***Correspondence:**
Dr. Maryam Abdullah Baik,
E-mail: maryam.abdullah.baik@gmail.com

ABSTRACT

Salbutamol is a well-known example of a short-acting beta agonist that is used as therapy for managing asthma, bronchospasm and chronic obstructive pulmonary disease. Short-acting beta agonist without a controller should only be taken into consideration as needed if symptoms are minimal and there is no asthma-related awakening. Salbutamol's maximal efficacy is based on how it is administered and the formulation that is utilized. Inhaled salbutamol is a first-line treatment for the majority of patients because it provides quick bronchodilation and typically relieves bronchospasm within minutes. Salbutamol immediately relieves the symptoms of acute asthma by relaxing the smooth muscle in the airways and boosting airflow. Patient experiences immediate relief from coughing, wheezing, tightness in the chest, and shortness of breath. Salbutamol's fast alleviation of symptoms may encourage abuse and overuse, especially in adolescents. On the basis of clinical and laboratory results, the diagnosis of salbutamol toxicity can be formed. The management is primarily supportive and includes stopping the harmful agent and using beta blockers to relieve symptoms. The purpose of this research is to review the available information about diagnosis, complication and treatment of acute salbutamol toxicity. Salbutamol overdose may cause tremors, hyperglycemia, lactic acidosis, and cardiac arrhythmias. Treatment for patients with severe symptoms include administration of beta-blockers if there are no contraindications also potassium supplementation, activated charcoal and gastric lavage among commonly used therapeutic strategies. Although salbutamol toxicity is uncommon still the physicians shall be knowledgeable about the diagnosis and management of salbutamol toxicity due to its widespread usage

Keywords: Salbutamol, Asthma, Treatment, Toxicity

INTRODUCTION

Salbutamol with the generic name of albuterol is a synthetic sympathomimetic amine that specifically activates beta-adrenoceptors. Albuterol, a racemic combination, has a short half-life and has moderate beta-2 adrenoceptor site selectivity. Through the activation of adenylate cyclase, beta adrenoceptor agonists promote the synthesis of cyclic adenosine monophosphate. Cyclic adenosine monophosphate causes smooth muscle relaxation and the suppression of mast cell discharge in the airways, as well as increasing the activity of the cyclic adenosine monophosphate protein kinase A. The beta-2 adrenoceptors in the bronchial tree, uterus, and vascular smooth muscles are more responsive to salbutamol than the beta-1 adrenoceptors in the heart. The primary pharmacological complication of salbutamol inhalation or oral administration is bronchodilation. With its ability to lower serum potassium levels, salbutamol can be used to treat hyperkalemia.[1]

Albuterol comes in a variety of formulations that are approved for the treatment of bronchospasm. For prompt symptom alleviation, a 2.5 mg nebulized solution administered two or three times per day as needed is adequate. The nebulized solution can also be dosed as needed at 1.25 to 5 mg every four to eight hours for rapid symptom relief. Depending on the patient, it is recommended to utilize one or two 90 mcg puffs every four to six hours with a powdered or aerosol metered-dose inhaler, but no more than 12 puffs in a 24-hour period. For pill and syrup forms, it is advised to take 2 to 4 mg every 6 to 8 hours, with a daily maximum of 32 mg. Depending on the patient's needs, the extended-release tablets are taken every 12 hours in doses of 4 mg or 8 mg, with a daily maximum of 32 mg.[2] There has been a plethora of instances of salbutamol toxicity when it has been consumed orally, but there have only been very few cases of salbutamol overdose when it has been inhaled. Due to the widespread usage of salbutamol, many individuals may have overdose symptoms, which can range from moderate side effects to severe toxicity and may go unnoticed by emergency medical professionals.[3]

One of the most common medications generating drug-induced tremor is salbutamol, which is frequently recommended for chronic obstructive pulmonary disease and asthma. In extensive clinical trials, 7%-20% of patients reported tremor caused by albuterol inhalation, and 14% of patients reported tremor caused by isoproterenol inhalation. Tremor and other side effects of beta 2-agonists seem to be dose-related.[4] As much as 20 times the usual daily dose of salbutamol did not result in any fatalities, as per an analysis of overdoses. Salbutamol overdose normally has mild, benign side effects, though they can last for a long time. Typically, the only cardiovascular effects are sinus tachycardia and expanded pulse pressure. Even though the diastolic pressure may decrease, the systolic pressure is kept constant by the increased cardiac output from tachycardia. With overall body potassium reserves typically staying normal, transient hypokalaemia caused by a transfer of extracellular potassium to the intracellular space can occur. Increased lactate production can result in brief metabolic acidosis. Salbutamol overdose frequently results in agitation, tremors, anxiety, vomiting, nausea, and dilated pupils.[5] The purpose of this research is to review the available information about diagnosis, complication and treatment of acute salbutamol toxicity

LITERATURE SEARCH

This study is based on a comprehensive literature search conducted on October 14, 2022, in the Medline and Cochrane databases, utilizing the medical topic headings (MeSH) and a combination of all available related terms, according to the database. To prevent missing any possible research, a manual search for publications was conducted through Google Scholar, using the reference lists of the previously listed papers as a starting point. We looked for valuable information in papers that discussed the information about diagnosis, complication and treatment of acute salbutamol toxicity**.** There were no restrictions on date, language, participant age, or type of publication.

DISCUSSION

Salbutamol raises heart rate firstly by reducing the duration of diastole, after being absorbed into the bloodstream, secondly, by acting on beta-adrenergic receptors in the heart, raising sympathetic outflow. Moreover, salbutamol is observed to alter the electrophysiology of the heart including atrioventricular delay and decreased atrial and ventricular refractoriness.[6] Due to the widespread usage of salbutamol, many people may develop mild to severe side effects as a result of overdosing. However, since intentional beta-agonist overdose is uncommon, symptoms could go unnoticed by medical professionals. The majority of beta-agonist adverse effects, including tachycardia, a prolonged QT interval, and dysrhythmia, affect the cardiovascular system. In addition to hypokalaemia, tremor, and lactic acidosis, salbutamol poisoning can also cause these side effects. The syndrome of beta 2-agonist toxicity should be known to all doctors because it might result in QT prolongation and sudden cardiac death.[7] It is not recommended to administer systemic salbutamol via intravenous infusion to asthma patients beyond the clinical studies due to its metabolic effects, which could exacerbate respiratory function in asthma. Consideration should be made to other therapy such non-invasive ventilation for patients who don't respond to systemic steroids, ipratropium, or inhaled beta 2-agonists rather than increasing the dosage potency or amount of a medication that could paradoxically make respiratory function worse.[8]

Diagnosis and management; evidence from literature

Clinical and laboratory investigations can be used to make the diagnosis of salbutamol poisoning. Salbutamol can produce tachycardia, tremors, and hypokalemia at high therapeutic doses. Additionally, hyperglycaemia, lactic acidosis, and cardiac arrhythmias might result from salbutamol overdose. Salbutamol toxicity is mostly treated by supportive measures. In the absence of contraindications, beta-blockers may be explored for very symptomatic patients. Advanced cardiac life support recommendations should be followed when treating cardiac arrhythmias. Since transcellular shift rather than a general body deficiency is the underlying mechanism, salbutamol-induced hypokalemia should only be treated sparingly, if at all. While salbutamol overdose is known to produce lactic acidosis as a side effect, physicians should thoroughly examine patients to look for other potential reasons. Patients with metabolic acidosis often exhibit hyperventilation. Hyperventilation is often a compensatory strategy for metabolic acidosis in the context of salbutamol toxicity rather than a symptom of increased respiratory distress necessitating more beta 2-agonist medication.[3]

Tomar and Vasudevan stated that when a child is wheezing, restless, tachycardic, and hyperglycaemic while receiving increasing doses of inhaled salbutamol and blood gas measurement reveals metabolic acidosis and hypocapnia with PCO_2 <35 Torr, indicating that the degree of airway obstruction has likely lessened enough to discontinue beta 2 agonist medication, the risk for beta agonist toxicity should be taken into consideration. It should notify the clinician that an urgent change in therapy is required to get rid of the symptoms. The early warning sign of salbutamol toxicity may be ketonuria. The clinician who decides to intensify treatment solely based on the patient's wheezing may actually make things worse for them. Since side effects are identical to the symptoms of asthma itself, care must always be taken when drawing conclusions about chronic or worsening respiratory distress owing to metabolic acidosis and hyperventilation in children treated with beta agonists. To determine the best course of care, it is crucial to implement the tapering strategy in a safe, intensive setting while using arterial blood gas analysis and considering the alveolo-arterial oxygen gradient.[9]

Results of a prospective study showed that the average amount of salbutamol that was reportedly consumed was 89 mg, and the average plasma concentration was 166 ng ml^{-1} (range 18-449 ng ml^{-1}). Plasma potassium was 2.9 on average. None of the study participants experienced significant cardiac dysrhythmias. Both the plasma salbutamol concentration and the plasma potassium concentration as well as the plasma salbutamol concentration and pulse rate showed statistically significant associations. Hence in individuals, without respiratory decompensation, supratherapeutic plasma salbutamol concentrations were tolerated without any fatalities or significant cardiac arrhythmias.[10] Yilmaz et al reported a case of a four-year-old girl who had salbutamol intoxication presented with agitation, trembling, sinus tachycardia, moderate hypokalemia, and hyperglycemia. The infant was visibly trembling, anxious, and had fever as well as a heart rate of 185 beats per minute at admission. Physical examination revealed no obvious ailment to account for her temperature. She was effectively managed with electrocardiogram monitoring, gastric lavage, activated charcoal, intravenous hydration, and other procedures. Throughout her hospital stay, her blood sugar, QT interval, and plasma potassium level were constantly monitored. Within 24 hours of admission, her temperature, tachycardia, serum potassium, and glucose levels all returned to normal, and she was discharged in good health.[11]

Danenberg reported the case of a 20-year-old asthmatic woman who consumed 30 g of paracetamol and 300 mg of salbutamol. She also had tremor, hypokalemia, hyperglycemia, sinus tachycardia up to 160 beats per minute, and low blood pressure measuring 80/50 mmHg. She was efficiently treated with gastric lavage, intravenous fluids, potassium, and N-acetylcysteine and within 24 hours, the symptoms disappeared.[12] Minton, Baird and Henry reported in their study that in placebo-controlled research, involving six healthy volunteers who received single oral doses of 8 mg of salbutamol, 40 mg of propranolol, 100 mg of atenolol, 8 mg of salbutamol plus 40 mg of propranolol, and 8 mg of salbutamol plus 100 mg of atenolol. Plasma potassium decreased after inhaling salbutamol and increased after inhaling atenolol or propranolol, and propranolol restored salbutamol's hypo-kalaemic impact more efficiently than atenolol. Blood glucose increased after taking salbutamol, but none of the other therapies had any effect on it. When combined with either beta-adrenoceptor antagonist, salbutamol plus propranolol caused a greater decrease in standing and lying pulse rates than when combined with salbutamol plus atenolol. After salbutamol, blood pressure increased, and it decreased after each of the other therapies. Thus, 40 mg of propranolol was just as effective at counteracting the metabolic effects of 8 mg of salbutamol as 100 mg of atenolol was at counteracting the cardiovascular effects. Propranolol should be taken into consideration as an antidote in cases of symptomatic salbutamol overdose, providing the patient does not have asthma.[13]

Habib et al reported a case of a 28-year-old-women who ingested 100 mg of salbutamol and was managed by administration of two subcutaneous injections of human regular insulin with a total dose of 20 units, two intravenous saline injections with potassium supplementation, activated charcoal, and gastric lavage. During the following 48 hours, serum glucose levels varied between 65 and 134 mg/dl, but they then returned to normal. Within 12 hours, serum potassium levels returned to normal, while urine ketone bodies vanished

within 48 hours. The following day, the pulse rate was under 100 beats per minute. She continued to fare well after being discharged on the third day, and over the four months of follow-up, her glucose levels were reported to be normal.[14] Chandrasekaran et al. reported theophylline and salbutamol overdosage in a 21-year-old- female. Investigations revealed severe metabolic acidosis, hypokalemia, and hypocalcemia that were treated with intravenous fluids, vasopressors, injections of calcium gluconate and potassium chloride, as well as blood tests that revealed hypocalcemia. She was started on 1.5 ml/kg of lipid emulsion as a bolus and then 0.5 ml/kg/h as an infusion because her hemodynamic condition did not improve. Her hemodynamic condition then steadily improved, and she was discharged after 24 hours. Lipid emulsion has been utilized in numerous tablet overdoses and local anaesthetics. In this patient, prompt lipid emulsion administration led to an early recovery from shock.[15] Jones and Taylor demonstrated a case of a 43-year-old asthmatic female with unstable asthma who was steroid-dependent and used salbutamol up to 30 times per day. Her asthma control significantly improved after cutting back on her beta-agonist use, and she was able to successfully cease taking oral steroids.[16]

Salbutamol toxicity if not managed and treated timely can lead to death and fatal complications as described by Boucher et al. who reported fatal salbutamol toxicity in a 36-year-old female asthmatic patient who after following unexpected collapse at home and acute dyspnea, passed away not long after being admitted to the hospital. Salbutamol overdose was confirmed by toxicological tests, and disclosed by necropsy findings of acute lung edema, significant right ventricular dysplasia, and acute lung edema. She was also pregnant. The existence of various pro-arrhythmogenic variables in combination, such as arrhythmogenic right ventricle dysplasia, hypoxemia associated to bronchospasm, and salbutamol overdose, point to the participation of an initial disturbance of the ventricular rhythm resulting in cardiac failure.[17] Majority of literature available comprises of case reports addressing salbutamol toxicity there is however further need of clinical studies based on larger sample size population to study the clinical manifestations, effective strategies for prompt diagnosis and management of salbutamol overdose as the present literature discussing the complication diagnosis and management is quite limited.

CONCLUSION

Salbutamol overdosage or toxicity is less commonly reported but still it is an important presentation to recognize. Clinical assessment and laboratory findings can aid the diagnosis while the management is chiefly supportive however due to prevalent use of salbutamol physicians shall be well aware of the diagnosis and management of salbutamol toxicity.

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