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Case Report

Cyanosis during Transesophageal Echocardiography that would Not Improve with Increased oxygen support: Revisiting an Important Clinical Lesson

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Abstract

Hypoxia that does not respond to increased oxygenation in the absence of cardiopulmonary causes in patients undergoing endoscopy procedure such as transesophageal echocardiography (TEE) should raise concern about the possibility of topical anesthesia induced methemoglobinemia. Though reported in literature previously, benzocaine induced methemoglobinemia is still an infrequent occurrence. Thus, high index of clinical suspicion is imperative for timely diagnosis and management of such patients.

Keywords: *Benzocaine; Methemoglobinemia; Trans Esophageal Echocardiography; Methylene Blue*

Introduction

Acquired methemoglobinemia due to topical use of benzocaine during transesophageal echocardiography (TEE) have been previously reported but is still infrequently encountered clinical scenario [1,2]. Hypoxia that does not respond to increased oxygenation, sudden onset of cyanosis after administration of agents which are potentially oxidative and abnormal blood color during phlebotomy should raise clinical suspicion of methemoglobinemia. Prompt diagnosis and management strategies should be initiated to avoid catastrophic outcomes.

Case Description

A 61-year-old female with past medical history of coronary artery disease, hypertension, diabetes, obesity and obstructive sleep apnea (OSA) was scheduled for TEE and cardioversion in view of new onset atrial fibrillation. Prior to the procedure, her vital signs were stable with oxygen saturation of 96% on room air. Her throat was sprayed with 21 second sprays of Cetacaine (Benzocaine 14.0%, Butamben 2.0% and Tetracaine Hydrochloride 2.0%). Adequate topical analgesia was achieved and adequate sedation was also achieved with 50 mg lidocaine IV and 40 mg propofol titrated over a period of time. After the TEE was completed, it was noted that the oxygen saturation was 79% with the bolus patient breathing infusion spontaneously supplemented with 4 Liter/min oxygen via nasal cannula. Fraction of inspired oxygen (FiO_2) was increased without any improvement in oxygen saturation. The patient soon regained consciousness and had no difficulty breathing and her fingernails and lips were noted to be dusky. Blood pressure and heart rate were stable. While fully awake there was still no improvement in oxygen saturation. Pulse oximeter probes and sites were changed without improvement. A trial of continuous positive pressure ventilation (CPAP) was also done because of her history of OSA. Chest auscultation revealed no abnormalities. The cardiologist confirmed that her ejection fraction was 60% and that she had no significant diastolic dysfunction. After 15 minutes

post-procedure, her oxygen saturation was fixed at 84 - 85%. An arterial blood gas (ABG) was sent along with blood for co-oximetry, which revealed a methemoglobin level of 39%. The cardioversion was postponed and methylene blue, 1 mg/kg, was started intravenously. The patient was transferred to the cardiac care unit. Over the next 30 minutes, the oxygen saturation improved to 96%. A repeat methemoglobin level came back as 1%. The patient remained stable and alert throughout this event. She was discharged home safely.

Discussion

Methemoglobin is an abnormal state of hemoglobin where the ferrous irons of heme are oxidized to the ferric state which cannot reversibly bind oxygen. As a result, patients with methemoglobinemia have a functional anemia and the circulating methemoglobin containing hemoglobin molecules are incapable of delivering oxygen resulting in impaired tissue oxygenation [3]. Risk factors for the development of methemoglobinemia include being a genetic carrier for cytochrome b5 reductase deficiency, leading to decreased enzyme levels that may become clinically relevant on administration of oxidizing drugs [4]. Topical anesthetic agents like benzocaine, lidocaine, prilocaine and medication like dapsone have been found to be the most common precipitating agents of acquired methemoglobinemia [5].

Cetacaine is a fast-acting, long lasting prescription topical anesthetic comprising Benzocaine 14.0%, Butamben 2.0% and Tetracaine Hydrochloride 2.0%. Cetacaine is primarily used to, ease discomfort and suppress the gag reflex during endoscopic procedures. Label on the bottle of Cetacaine mentions that each 200 mg dose of Cetacaine spray contains 28 mg of benzocaine, 4 mg of butamben and 4 mg of tetracaine HCl. Benzocaine is its component that has been found to be associated with methemoglobinemia [1,5]. 2006 US Food and Drug Administration (FDA) Public Health Advisory and a 2011 Safety Announcement have stressed about severe cases of benzocaine induced methemoglobinemia. According to a safety announcement published on 04-07-2011, FDA received total 319 cases of methemoglobinemia associated with the use of benzocaine sprays. 7 cases of death were implicated to benzocaine induced methemoglobinemia while 32 cases were defined as life threatening with methemoglobin level greater than 55% [6]. There have been few studies conducted which show that cases of benzocaine induced methemoglobinemia are still uncommon. 19 out of 28,478 (0.07%) patients who underwent TEE were found to have a high mean peak methemoglobin level in a study [2] while no statistically significant difference was found between two groups undergoing esophagogastroduodenoscopy with and without a single one-second pharyngeal spray of 20 percent benzocaine in another study [7].

Initial symptoms of methemoglobinemia include cyanosis and resultant pale, gray or blue colored skin, lips, and nail beds. Patients can have dizziness, headache, tachycardia, dyspnea, and lethargy. Respiratory depression, encephalopathy, coma, seizures, and death may occur at higher levels of methemoglobin. Cyanosis becomes apparent with more than 1.5 gram/deciliter (equivalent to 8 to 12% of normal hemoglobin level) of methemoglobin concentration while it can be fatal if levels reach above 30% [8]. Suspicion should be high with the sudden onset of hypoxemia on administration of implicated agents, in cases of hypoxemia that do not improve with increased fraction of inspired oxygen, or in cases of hypoxemia with abnormal coloration of blood with phlebotomy, which has been described as chocolate-colored in the literature. Diagnosis should be confirmed via co-oximetry [9]. Routine pulse oximetry is unreliable given the absorption spectrum of methemoglobin resulting in a reading of 85% independent of true oxygen saturation [10]. Therapy is indicated if the patient is symptomatic or if levels of methemoglobin are found to be > 20% of total hemoglobin. While no randomized clinical trials exist comparing methylene blue to placebo in the treatment of acute acquired methemoglobinemia, it remains the treatment of choice. Methylene blue acts as an extrinsic electron acceptor in the NADPH-dependent reduction of methemoglobin [9]. Ascorbic acid has been used in cases where methylene blue has not been available or in cases when methylene blue is contraindicated, resulting in modest reduction in methemoglobin levels after 24 hours (compared to onset of action of 10 to 60 minutes for methylene blue) [11].

Conclusion

Cyanosis and hypoxemia that do not respond to increased oxygenation in the absence of cardiopulmonary causes in patients undergoing endoscopy procedure such as TEE should raise suspicion about the possibility of topical anesthesia induced methemoglobinemia.

Though reported in literature previously, benzocaine induced methemoglobinemia is still an infrequent occurrence. Thus, high index of clinical suspicion is imperative for timely diagnosis and management of these patients. Routine pulse oximetry and arterial blood gas analysis are unreliable in such cases. Co-oximetry is effective in confirmation of diagnosis and prompt administration of intravenous methylene blue has been found to be highly effective treatment option.

Conflict of Interest

Authors declare no conflict of interest.

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