Toxic Ingestion of Ammonium Nitrate in the Setting of Small Bowel Obstruction

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Received date: May 24, 2017, Accepted date: June 02, 2017, Published date: June 10, 2017

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Abstract

Methemoglobinemia after ingestion of ammonium nitrate can lead to significant morbidity and mortality in affected patients. Ammonium nitrate is a primary ingredient in synthetic “cold packs,” which are used in healthcare as a substitute for bags of ice. Acute or chronic ingestion can have serious consequences to patient health including isosmotic diuresis, metabolic acidosis, circulatory collapse and gastritis. Methemoglobinemia is a result of nitrite toxicity. This toxicity can be compounded by patient comorbidities, which may further complicate treatment. Rapid and accurate diagnosis is essential in the treatment of Methemoglobinemia following ammonium nitrate ingestion.

We present the case of a 76 year-old woman who was admitted for small bowel obstruction (SBO) and unintentionally ingested the contents of a cold pack. The patient subsequently became tachycardic, hypotensive, and unresponsive requiring urgent resuscitation and management in the ICU setting. Methemoglobin levels were elevated. The patient was treated with methylene blue (MB) and made a full recovery.

Introduction

Methemoglobin forms when the ferrous (Fe2+) form of heme in hemoglobin is oxidized to the ferric (Fe3+) state. Ferric heme is unable to bind oxygen, and the remaining ferrous heme develops increased oxygen affinity. This causes impaired oxygen delivery to tissues, resulting in a “left shift” in the oxygen dissociation curve [1].

The formation of methemoglobin occurs naturally in healthy individuals at a slow rate and is corrected via a NADH-dependent reaction catalyzed by cytochrome b5 reductase [2]. The oxidative process that converts normal hemoglobin into the ineffective methemoglobin can also occur pathologically via congenital abnormalities such as Hemoglobin M disease or from an external source as seen with some medications like Dapsone [3,4]. Another cause, though uncommon, occurs following the ingestion of ammonium nitrate, which can be found in commercially available cold packs. Methemoglobinemia from such toxic ingestions is known as acute acquired methemoglobinemia.

Healthy individuals receive nitrate via the diet or endogenous sources. Humans lack effective nitrate reductase enzymes and therefore the reduction of nitrate to nitrite is performed by the intestinal flora. Following the formation of nitrite, it can be further reduced to nitric oxide (NO) by way of hemoglobin or myoglobin [5]. Furthermore, the production of NO via these and other pathways is increased during periods of acidosis or hypoxia such as in the case of severe small bowel obstruction [6]. Nitrite reduction to NO and NO-modified proteins during physiological and pathological hypoxia may contribute to vasodilation, modulation of cellular respiration and the cellular response to ischemic stress [7].

Case Report

A 76-year-old female with a history of COPD (40 pack year smoking history), hypertension, and a prior primary SBO presented with two weeks of abdominal pain and diminished bowel function, which had worsened over the previous two days. The patient's previous SBO had occurred secondary to a closed-loop obstruction from an adhesive band and was treated with an ileocolic resection. On presentation to the emergency department, she was afebrile with stable vital signs. On physical exam, the patient was cachectic, in no acute distress, alert, and oriented. Her abdomen was moderately distended and water, the patient opened the cold pack and drank several sips of its contents. Poison control was contacted and advised no intervention.

Later that evening, the patient became tachycardic with a heart rate in the 130s, hypoxic with an oxygen saturation of 86% on room air, and hypotensive with a systolic blood pressure in the 80s. She remained hypoxic despite 100% FIO2 and a PEEP of 7 and required manual bagging to maintain oxygen saturation. Phenylephrine was administered to manage the patient's hypotension.

On hospital day 2, the patient complained of abdominal pain and was given a cold pack by nursing staff. Thinking it was filled with ice and water, the patient opened the cold pack and drank several sips of its contents. Poison control was contacted and advised no intervention. Later that evening, the patient became tachycardic with a heart rate in the 130s, hypoxic with an oxygen saturation of 86% on room air, and hypotensive with a systolic blood pressure in the 80s. She was immediately evaluated by the surgical team, and subsequently became unresponsive with worsening desaturation and tachycardia. The code team was called and the patient was emergently intubated. She remained hypoxic despite 100% FIO2 and a PEEP of 7 and required manual bagging to maintain oxygen saturation. Phenylephrine was administered to manage the patient's hypotension.

Labs were drawn, and the patient's blood was noted to be unusually dark. Venous blood gas (VBG) that evening demonstrated a pH of 7.24, lactate of 15, pCO2 of 35, pO2 of 50, and a HCO3 of 14. Of note, there was a discrepancy between the basic metabolic panel chloride and...
level (within normal limits) and that of the blood gas (chloride greater than 120).

The patient was managed in the surgical intensive care unit and had improvement in her respiratory status, hemodynamic stability, and laboratory values overnight. A methemoglobin level was drawn the following morning, with a value of 22%. Methylene blue (MB) was then administered at a dose of 1-2 mg/kg over 5 minutes.

The patient demonstrated increased abdominal tenderness with diffuse guarding and therefore underwent an exploratory laparotomy. She was found to have dense adhesions with an obstruction at the previous anastomosis. A secondary ileocolic resection was performed. The patient recovered well and was extubated on post-operative day 2. She did well, regained bowel function, her diet was advanced, and she was discharged home.

Discussion

Methemoglobinemia may result from a variety of conditions, congenital and acquired, leading to the creation of ferric heme. Acquired forms of methemoglobinemia have been shown to follow administration of commonly used medications such as dapsone (used in pneumocystis prophylaxis), benzocaine (topical anesthetic), or nitric oxide (pulmonary hypertension treatment) [8-10]. Other cases detail methemoglobinemia following the application of silver nitrate to burn areas in some patients and in infants after drinking water high in inorganic nitrates [11,12]. Rarely, however, this phenomenon can be observed in patients as a result of ingesting the contents of medical cold packs.

Cold packs are used in hospitals every day in order to provide comfort via cooling to painful or swollen areas in afflicted patients. Ammonium nitrate is a major ingredient in these packs. Ammonium nitrate is an acidifying salt with diuretic effects that is readily absorbed in the GI tract. After entering the circulation, ammonium ions are largely converted to urea in the liver [11]. This conversion to urea generates hydrogen ions leading to a metabolic acidosis [13]. Additionally, urea contains a nitrate ion which, when excreted in the urine along with an equal amount of sodium or potassium and an isosmotic quantity of water, creates a diuresis11. Interestingly, it is because of this diuretic effect that ammonium nitrate was used in the 1920s in the treatment of pulmonary edema [14]. There is one published case series documenting cold pack ingestion in the published literature [11]. This series details complications in 6 patients following consumption of ammonium nitrate at a dose of 6-12 grams/day, most commonly gastritis [9]. In addition to causing the aforementioned symptoms, once ingested, inorganic nitrates can be converted to nitrates by bacteria in the skin or GI tract. Once the nitrite is created, it has the ability to oxidize the ferrous form of hemoglobin, creating methemoglobin.

Methemoglobin is the oxidized Fe3+ (ferric) form of hemoglobin and, as such, does not bind to oxygen efficiently [12]. As a result of the reduced binding capacity of oxygen to the ferric heme, delivery of oxygen to the tissues is reduced creating a "left shift" in the oxygen dissociation curve leading to a functional anemia. Therefore, signs and symptoms of methemoglobinemia are largely a function of the acute impairment of oxygen delivery to tissues. The primary clinical characteristic of methemoglobinemia involves cyanosis, which is unresponsive to oxygen therapy with increased fraction of inspired oxygen (FiO2) [15]. Early symptoms include pale-gray or a bluish discoloration to the patient’s lips, nail beds, and skin. Cyanosis is clinically detected when the absolute concentration of Methemoglobin exceeds 1.5 g/dL (8-12%) methemoglobin at normal hemoglobin concentrations). Lightheadedness may also occur with the patient complaining of headache, tachycardia, dyspnea, and lethargy may occur at levels less than 30%. Gastritis may also be seen in some cases. At higher Methemoglobin levels (55-70%), reduced consciousness, cardiac arrhythmias, circulatory collapse from vasodilation, neurological depression, and even death may occur. We suspect that a methemoglobin level drawn during our patient’s acute decompensation would have been in the higher range. Vasodilation specifically may occur following the reduction of nitrite to NO3.

We present the only published case of ammonium nitrate toxicity in a patient with an SBO. Ammonium nitrate is readily absorbed from the GI tract, and toxicity may be worsened in patients with GI dysfunction. Additionally, the creation of NO may be augmented during periods of acidosis or hypoxia such as in our patient in the setting of obstruction and nasogastric tube decompression [6]. These factors likely contributed to the circulatory collapse seen in our patient and lead to a more dramatic deterioration.

Diagnosis of acute methemoglobinemia requires early recognition of the symptoms including cyanosis, hypoxia, or lethargy. Without a known history of ingestion of ammonium nitrate, clinical detection may be difficult given the non-specific nature of the symptoms. Discoloration of blood may also be seen ranging from dark red or blue to chocolate brown. Furthermore, unlike deoxyhemoglobin, the abnormal color does not dissipate after exposure to air [16]. A methemoglobin level should be obtained in order to gauge severity and monitor response to treatment. Monitoring patients with methemoglobinemia via pulse oximetry can be inaccurate as methemoglobin absorbs light at the pulse oximeter’s two wavelengths. Regardless of the actual hemoglobin oxygen saturation, high levels of methemoglobin can cause the oxygen saturation to display values of approximately 85% [17]. Since arterial blood gas analysis measures arterial oxygen partial pressure, the levels of oxygen saturation can be falsely normal in patients with methemoglobinemia although this was not the case in our patient. Still, blood gas readings can be helpful in determining the acid base status of the patient and thus should be followed.

Treatment should first include discovery of the offending agent and removing or discontinuing its use. Causal factors include dapsone, aniline dyes, some topical anesthetics, and water with elevated nitrate levels [10]. Management of the hemodynamic consequences of methemoglobin toxicity is also vital given the vasodilatory effects of NO and the diuretic effects of ammonium nitrate [5,14]. Fluid resuscitation and administration of vasopressors may be necessary as they were for our patient. Asymptomatic patients, often with methemoglobin levels <20%, may require no treatment. However, the preferred method in symptomatic patients is MB. MB provides an artificial electron transporter for the ultimate reduction of methemoglobin via a NAPH-dependent pathway. Dosing for MB is recommended at 1-2 mg/kg given intravenously over a 5-minute period. This dosing can be given a second time one hour later if methemoglobin levels remain elevated [18]. Because of its oxidizing potential, repeated doses of MB at a dose of 2 mg/kg can lead to hemolysis even in patients with normal G6PD levels and therefore should be avoided [19]. Ascorbic acid may be used in patients with glucose-6-phosphate dehydrogenase deficiency (G6PD), as MB requires NADPH in order to become activated and is deficient in G6PD individuals [20]. Ascorbic acid is an electron donor and can
therefore directly reduce methemoglobin [21]. Dosing for ascorbic acid in patients with G6PD is 300-1000mg per day orally in divided doses. In most patients, MB is preferred to ascorbic acid because of its rapid onset of action [17,22].

When methemoglobinemia is treated effectively, patients improve rapidly. Repeat measurements of methemoglobin levels are reasonable, but not necessary if the patient continues to improve clinically and cyanosis has resolved.

Conclusion

Methemoglobinemia following ingestion of ammonium nitrate found in cold packs is an uncommon occurrence, with only 6 cases reported in the literature. A high index of suspicion, good history taking and understanding of the clinical clues are essential in making a rapid diagnosis and preventing patient morbidity and mortality. Patients with bowel dysfunction should undergo immediate nasogastric tube decompression and be closely monitored. Additionally, patients with severe SBO present a unique difficulty as the patient may be acidic, which can lead to further NO production and subsequent vasodilation and circulatory collapse. Methemoglobin levels can aid in making the diagnosis. Pulse oximetry is not, however, a good indication of the severity of methemoglobinemia and should not be used alone in evaluating the patient's status. Similarly, blood gas values may show acid-base imbalances in patients with methemoglobinemia, but can also be inaccurate in demonstrating patient progress. MB or ascorbic acid are effective treatments in the acute setting, but should not be given too liberally as they harbor a significant side effect profile. Repeat measurement of methemoglobin levels are useful in monitoring resolution of illness, but are not always necessary as clinical improvement is often sufficient to determine the necessity of continued treatment. With prompt diagnosis and management, patients with acute acquired methemoglobinemia typically make a rapid and complete recovery.

References