Journal of Clinical Toxicology
ISSN: 2161-0495

Faley and Chase, J Clinic Toxicol 2012, 2:4
DOI: 10.4172/2161-0495.1000127

Case Report Open Access

A Case of Severe Amyl Nitrite Induced Methemoglobinemia Managed with Methylene Blue

Brian Faley[1,2,*] and Howard Chase[3]

[1]*Clinical Assistant Professor, Ernest Mario School of Pharmacy of Rutgers University, 160 Frelinghuysen Rd, Piscataway, NJ 08854, USA*
[2]*Clinical Pharmacist, Emergency Medicine, Hackensack University Medical Center, 30 Prospect Ave., Hackensack, NJ 07601, USA*
[3]*Department of Emergency Trauma, Hackensack University Medical Center, 30 Prospect Ave., Hackensack, NJ 07601, USA*

Abstract

Introduction: It is well documented that amyl nitrite can cause methemoglobinemia [1-7]. This condition can be successfully treated with methylene blue therapy [1-8]. Amyl nitrite is used therapeutically as part of the antidote cocktail to treat cyanide poisoning; however, it also carries a high abuse potential.

Case Report: A 45 year old male with a history of hypertension, polysubstance abuse, and anxiety was found unconscious. Upon Arterial Blood Gas (ABG) collection, the blood appeared chocolate brown and a methemoglobin level of 75.4% was revealed along with a carboxyhemoglobin level of zero. Methylene blue was administered as a single weight based bolus and the patient's methemoglobin level eventually returned to normal.

Discussion: Many drugs are known to cause methemoglobinemia, but few are abused. An exception is amyl nitrite. Recently, the Food and Drug Administration (FDA) issued a safety notice [5] warning practitioners about the risk of serotonin syndrome when methylene blue is utilized concomitantly with medications exhibiting serotonergic effects.

Conclusion: In light of the new safety warning issued by the FDA, the clinician should be familiar with the dosing and administration of methylene blue as well the appropriate ways to manage or avoid potentially serious adverse events associated with its use.

Keywords: Methemoglobinemia; Methylene Blue; Amyl Nitrate

Introduction

It is well documented that amyl nitrite can cause methemoglobinemia [1-7]. This condition can be successfully treated with methylene blue therapy [1-8]. Amyl nitrite is used therapeutically as part of the antidote cocktail to treat cyanide poisoning; however, it also carries a high abuse potential. Amyl nitirite is know by the street names of Rush, Liquid gold, Locker room, and Snappers, as well as others. Methemoglobin levels of greater than 20% require treatment with methylene blue at a dose of 1-2 mg/kg. Previous case reports have shown that methemoglobin levels of greater than 70% require multiple doses of methylene blue therapy [4, 7]. We report a case illustrating one of the highest reported methemoglobin levels induced by amyl nitrite that is successfully treated with a single dose of methylene blue.

Case Report

A 45 year old male with a history of hypertension, polysubstance abuse, and anxiety was found unconscious for an unknown period of time in a parking lot. A call was placed to 911 and upon arrival of emergency medical services, the patient was unresponsive, appeared blue and was intubated with out medications due to his severe cyanosis. In addition, a 0.4 mg bolus of naloxone was administered intravenously with no response. During transportation to the emergency room, the patient became very combative and sedation with a midazolam bolus and infusion was initiated to maintain the patient's Endotracheal (ET) tube. Vital signs upon arrival included a temperature of 96.5 F, a blood pressure of 101/52, a pulse rate of 125 beats per minute, and a respiratory rate of 18 breaths per minute. The patient's pulse oximetry reading was not detectable despite the administration of 100% FiO_2 via ET tube. The patient's physical exam was normal with the exception of 1 mm pupils that were minimally reactive, clubbing of the hands and toes, and severe cyanosis. Labs drawn included an arterial blood gas (ABG), complete blood count, complete metabolic panel, lactate, blood alcohol, acetaminophen, aspirin, and ethylene glycol level were drawn. The ABG revealed a pH of 7.26, a PO_2 of 594.2 mmHg, an HCO_3 of 16.4 mmol/L, and an oxygen saturation of 100% In addition, the blood appeared chocolate brown and a methemoglobin level of 75.4% was revealed along with a carboxyhemoglobin level of zero. The patient's lactate level was 8.3 mmol/L. His urine drug screen was negative. All other labs were within normal limits. Both the head CT and the chest x-ray returned within normal limits as well. At this time, therapy was initiated with activated charcoal and polyethylene glycol as a precaution in the case of co-ingestion. Methylene blue was initiated as an IV bolus dose of 100 mg. The dose of methylene blue was based on an estimated weight of 80 kg. The patient's cyanosis immediately began to improve. Two hours after methylene blue administration, the patient's methemoglobin level was 9.4%. Two hours later, the patient awoke and began to pull at the ET tube. At this time, the patient was extubated. Upon awakening, the patient claims to have been in his usual state of health until earlier in the afternoon when he inhaled amyl nitrite. The patient claims to remember only utilizing two inhalations. His next memory is being intubated by EMS. He states that he has a history of alcohol abuse and that he will be completing a rehabilitation program in two weeks. He also has a history of abusing both narcotics

***Corresponding author:** Dr. Brian Faley, 30 Prospect Ave, Hackensack, NJ 07601, USA, Tel: 201-996-2928; Fax: 201 996 4910; Email: bfaley@humed.com

Received may 16, 2012; **Accepted** June 21, 2012; **Published** June 23, 2012

Citation: Faley B, Chase H (2012) A Case of Severe Amyl Nitrite Induced Methemoglobinemia Managed with Methylene Blue. J Clinic Toxicol 2:127. doi:10.4172/2161-0495.1000127

and cocaine that lasted for five to ten years, but states he has not been using either for the past two years. He currently takes unknown doses of clonidine, metoprolol succinate, and quetiapine. Forty eight hours later, the patient's labs all returned to normal and the patient decided to leave the hospital against medical advice.

Discussion

Many drugs are known to cause methemoglobinemia, but few are abused. An exception is amyl nitrite. Amyl nitrite is a part of the street drug class known as poppers, which got their name from the sound made when one of the glass ampules was opened [8]. The abuse potential for this drug is large for many reasons. Amyl nitrite causes a short lived euphoric feeling due to its ability to dilate blood vessels as well as induce tachycardia. It has also been suggested that amyl nitrite enhances sexual pleasure [9]. No laboratory assay is readily available to measure amyl nitrite levels. Given this high abuse potential, it is surprising that there were fewer than 60 calls to poison control centers in the US during 2009 related to the use of poppers [2]. This is probably due to the lack of obvious toxicity when used recreationally. However, when abused repeatedly, consequences can become quite severe. In 2009, the American Association of Poison Control Centers reported one death attributed to the use of poppers [2]. A case of status epilepticus associated with methemoglobinemia has also been reported [3].

Amyl nitrate, as well as other oxidizing agents, induces methemoglobinemia by converting the ferrous (Fe^{2+}) iron molecule found in normal hemoglobin to its ferric (Fe^{3+}) state, impairing its oxygen carrying capacity and causing both cyanosis as well as dark colored blood. Toxicity may only manifest when an oxidizing agent overwhelms the major enzyme responsible for converting methemoglobin back to hemoglobin, NADH Methemoglobin Reductase. Nicotinamide-Adenine Dinucleotide Phosphate (NADPH) is a minor pathway for the reduction of methemoglobin. However; the NADPH pathway can be augmented if it is provided with electron carriers [1].

Methylene blue remains the treatment of choice for methemoglobinemia. The mechanism to reduce toxicity is by reducing the methemoglobin back to hemoglobin thus increasing the oxygen carrying capacity back to normal levels. Methylene blue acts on the NADPH enzyme to exert its effects. Methylene blue donates electrons to the NADPH pathway and thus increases its ability to reduce methemoglobin back to hemoglobin [1]. NADPH is produced using G6PD and therefore in patients with a G6PD deficiency, methylene blue may be ineffective. Adverse events associated with the use of methylene blue include hypertension, confusion, anemia and serotonin syndrome. In July 2011, the Food and Drug Administration (FDA) issued a safety notice [5] warning practitioners about the risk of serotonin syndrome when methylene blue is utilized concomitantly with medications exhibiting serotonergic effects such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and others. This risk is due to methylene blue's reversible inhibition of monoamine oxidase A. The FDA recommends [5] that for non-emergent use of methylene blue, most agents should be discontinued 2 weeks prior to its' administration and can be reinitiated 24 hours after the last methylene blue dose. In the case of emergent administration, such as methemoglobinemia, serotonergic medications should be discontinued immediately and patients receiving methylene blue should be closely observed for hours after the last dose of methylene blue has been administered.

In the case presented here, these authors believe that the patient under reported the amount of amyl nitrate that he utilized. However, no work up was under taken to asses for genetic abnormalities that may have explained why only 2 inhalations may have caused such an abnormally elevated methemoglobin level. Another caveat to this case has to due with the use of single dose methylene blue. We believe that the patient responded to a single dose due to the short half life of amyl nitrate. Clinicians should not expect to see the same results with methylene blue for longer acting agents known to cause methemoglobinemia such as the topical anesthetics or dapsone.

Conclusion

This report illustrates that a clinician must include methemoglobinemia in the differential diagnosis of any patient that presents with severe cyanosis that is unresponsive to oxygen therapy. In light of the new safety warning issued by the FDA, the clinician should also be familiar with the dosing and administration of methylene blue as well the appropriate ways to manage or avoid potentially serious adverse events associated with its use.

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