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

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Abstract

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

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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 nitrate. Amyl nitrate 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 nitrate 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 nitrate enhances sexual pleasure [9]. No laboratory assay is readily available to measure amyl nitrate 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 (Fe²⁺) iron molecule found in normal hemoglobin to its ferric (Fe³⁺) state, impairing its oxygen carrying capacity 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 assess 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 as the appropriate ways to manage or avoid potentially serious adverse events associated with its use.

**References**

5. Food and Drug Administration (2011) FDA Drug Safety Communication: Serious CNS reactions possible when methylene blue is given to patients taking certain psychiatric medications.