In this case study, a single administration of methylene blue resolved significant amyl nitrate intoxication and critical methemoglobinemia. A 26-year-old female with no known medical history presented via EMS to the emergency department at an urban community hospital in Chicago, Illinois, with the chief complaint of intoxication after falling at a local bar and sustaining a possible syncopal event. The patient was transported on her own volition and was able to ambulate on arrival.
On initial examination, the patient had a temperature of 36.7 C, heart rate of 88 beats/min, blood pressure of 121/88 mmHg, respiratory rate of 18 breaths/min, and O2 saturation of 96% on room air. Her bedside serum glucose measurement was 125 mg/dl. She was visibly intoxicated, but alert and oriented to person, place and time. Her Glasgow Coma Scale (GCS) on arrival was calculated to be 15; she denied any loss of consciousness or other acute complaints. The physical exam did not have any overt signs of trauma. The ED staff decided to clinically observe her in the department until she met the criteria for clinical sobriety because she did not have safe transportation home.

One Hour Later
Approximately 65 minutes later, the patient was re-assessed and found to be unresponsive and cyanotic. Repeat vitals at that time revealed a BP of 115/65mmHg, HR of 146bpm, RR of 12, T of 35.7 C, and SpO2 of 88% on RA. Her GCS was recalculated at 6 (eye opening-1, verbal response-1, motor response-3), and she had a positive gag reflex, but significant pooling of secretions near her oral cavity.

The patient was immediately intubated secondary to her respiratory compromise, using rapid sequence intubation with 10mg IV etomidate and 30mg IV rocuronium (her weight was estimated at 50kg). The remainder of her physical examination was notable just for a grayish-blue hue to her skin, and her pupil exam was 2mm and sluggishly reactive to light. Labs drawn at this time included a complete blood count (CBC), comprehensive metabolic profile (CMP), serum lactate, blood alcohol level (BAL), troponin, urinalysis (UA), urine drug screen (UDS), serum salicylate and acetaminophen concentrations.

Her repeat glucose prior to intubation was 164 mg/dl. An arterial blood gas was drawn and revealed a chocolate-colored specimen with the following values: pH 7.36, pCO2 26, pO2 325 (on 100% fiO2), a calculated HCO3- of 12.8, O2 saturation of 95.1%. A methemoglobin Hb level was also sent, and MetHb resulted at 80.5%.

Further laboratory workup revealed a lactate of 11.8, CMP significant for
creatinine of 1.16 mg/dL and otherwise unremarkable, a BAL of 243, and UDS positive for methamphetamines. CBC, UA, troponin, salicylate and acetaminophen levels were within normal limits. The electrocardiogram (ECG) revealed profound S-T depressions infero-laterally with associated sinus tachycardia at a rate of 147bpm. Chest radiograph and CT scan of the head without contrast were unremarkable.

At this juncture, the state poison control center was consulted, who recommended a 2mg/kg IV bolus of 1% methylene blue for empiric antidotal therapy for methemoglobinemia. The patient was given a 100mg IV bolus and within 45 minutes had gradual improvement of pulse oximetry with saturations improving to 90-92% on 60% fiO2. A repeat arterial blood gas 45 minutes after methylene blue administration revealed a pH of 7.22, pCO2 34.9, pO2 of 74.9, HCO3- of 13.8, O2 saturation of 93.1%, MetHb% of 47.9, and a lactate of 6.6. Clinically, the patient had a marked improvement in her cyanosis, and also was starting to respond to commands with minimal sedation on the ventilator.

**Case Discussion**

It is well documented that amyl nitrate abuse can cause methemoglobinemia [1-20]. Amyl nitrate inhalants are well documented as recreational drugs that are used for both their vasodilatory tumescent effect and their transient feeling of “getting high,” giving the inhalant high abuse potential.

These inhalants often are marketed in glass vials that, when crushed, give them a characteristic sound – spawning the street name “poppers.” Individuals with significant nitrate inhalant-associated methemoglobinemia present clinically with cyanosis, acute respiratory compromise, and central nervous system depression.

Methemoglobin concentrations that exceed 20% are most commonly associated with somatic symptoms like headache, dyspnea, syncope and palpitations. The treatment for symptomatic methemoglobinemia is intravenous (IV) 1% methylene blue administered at a dose of 1-2 mg/kg; this can be repeated at 1mg/kg after 30 minutes if the MetHgb
percentage is not reduced to less than 20% after the first administration [30]. Previous case reports have noted that MetHb levels greater than 70% have required multiple administrations of IV methylene blue [3,20,21]. This particular case represents the highest recorded methemoglobin level in our thorough reading of the literature; it is especially surprising that only one dose of IV methylene blue was needed to resolve symptoms.

**Case Conclusion**

At approximately one hour and 50 minutes after initial discovery of respiratory compromise, another repeat ABG revealed a pH of 7.24, pCO2 of 39.9, pO2 of 354 (the patient had been put back on 100% fiO2 secondary to her mild hypoxia on the previous ABG), HCO3- of 14.6, O2 saturation of 99.1%, MetHb% of 14.6%, and a lactate of 4.4. Vital signs at this interval revealed a P of 116, RR 17, BP 105/55, and peripheral pulse oximetry of 95%. A repeat EKG done at this time revealed resolution of the previously mentioned S-T depressions.

The patient was fully aroused at this juncture but was started on a continuous midazolam infusion secondary to increasing combativeness against the ventilator. She was transferred to the intensive care unit (ICU) at approximately two hours and twenty minutes after initial respiratory compromise; on arrival in the ICU, a repeat basic metabolic profile showed an improvement in her creatinine to 0.47 mg/dL. All other repeat diagnostic studies were unremarkable.

The patient was extubated approximately seven hours after being intubated, with a post-extubation gas revealing a pH of 7.32, pCO2 of 32 pO2 of 102 on room air, with an associated MetHb% of 2.2. On repeat examination, the patient was alert and oriented x 3 but had no memory of the incident. She did remember drinking heavily the day before and using amyl nitrate poppers but could not remember the exact quantity.

**Methemoglobin and Amyl Nitrate**

Methemoglobin is formed by oxidation of the heme molecule from the Fe2+ (ferric) to the Fe3+ (ferrous) state via an NADPH-dependent pathway. This oxidized form is incapable of oxygen transport.
Furthermore, this oxidized heme molecule is altered in confirmation from its normal state, and thus has decreased ability to off-load oxygen to peripheral tissue [22]. There are known genetic causes of congenital methemoglobinemia, most notably erythrocyte methemoglobin reductase, pyruvate kinase, and G6PD deficiencies [25]. Secondary or acquired causes of methemoglobinemia occur secondary to the oxidation of exogenous substances such as local anesthetic agents including phenazopyridine (Pyridium®), sulfonamides, phenacetin, and dapsone [26-28].

Aliphatic esters such as amyl nitrate have been documented as common recreational agents that can precipitate methemoglobinemia [28]. They have high abuse potential secondary to their vasodilatory properties and reflex tachycardia, which often creates feelings of euphoria and enhanced sexual pleasure [18]. Even though the drug has been well documented as a cause of significant morbidity, its lack of immediate toxicity as well as its prevalence and availability make it a drug that is often overlooked for its significant abuse potential. Common side effects of administration include dizziness, syncope, nausea, and reflex tachycardia. Associated morbidity that has been reported in the literature includes macular retinopathy [23] and status epilepticus [24].

**EP Requirement: High Clinical Index of Suspicion**

The emergency physician often has a difficult task in determining this diagnosis in patients who present to the emergency department with altered mental status. The prevalence of acute alcohol intoxication makes this even more difficult, as in this case, because it can often mask other serious underlying processes. The emergency department provider should have a high clinical index of suspicion for acute methemoglobinemia secondary to recreational drug abuse if the patient presents as with our case: suspicion of acute intoxication secondary to recreational drug abuse, central cyanosis unresponsive to oxygen supplementation and central nervous system depression. In a comprehensive review of volatile nitrate-related methemoglobinemia, Hunter et al. created a clinical correlation between methemoglobin
percentage in blood and clinical signs with any with MetHb% between patient 50-70% exhibiting tachypnea, metabolic acidosis, seizures, dysrhythmias, central nervous system depression, coma and >70% showing symptoms consistent with severe hypoxia and death [22].

Standard pulse oximetry is often not a reliable indication of hypoxia as it only records levels of oxyhemoglobin and deoxyhemoglobin and generally patients will be saturating at approximately 85% despite supplemental oxygen. To our knowledge, our case is also the first to report evidence of demand strain to the heart as evidenced by the acute S-T depressions on EKG.

In any case severe respiratory compromise secondary to nitrate abuse and associated methemoglobinemia, the first intervention should be securing the patient’s airway. The definitive treatment is intravenous 1% methylene blue 1-2mg/kg administered over 3-5 minutes. IV methylene blue acts in the NAPDH reductase pathway to regenerate ferrous heme back from the ferric state.

As previously noted, the NADPH reductase enzyme is absent in those with G6PD deficiency thus making this treatment ineffective for those individuals. Adverse effects of methylene blue administration include hypertension, confusion, and anemia. In addition, serotonin syndrome has been reported to be associated with its use secondary to irreversible inhibition of monoamine oxidase A (MAO). Concomitant use of methylene blue is contraindicated in patients using MAO inhibitors; in these instances other therapies, such as exchange transfusion or hyperbaric oxygen may be sought.

Previous reports have suggested that levels greater than 70% MetHb will require repeat administrations of IV methylene blue, with a noted nadir less than 20% being significant for methemoglobinemia resolution [3,20,21]. Our case is unique in that it required only a single administration of the antidote to bring the patient’s MetHgb percentage down to a safe level. This may suggest that supportive care and aggressive resuscitation might allow only a single administration of methylene blue thereby
reducing the chance of side effects. Once a level less than 20% MetHb is achieved, one should expect clinical signs of improvement including prompt resolution of cyanosis, and increased alertness.

REFERENCES


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