

A Case Report of Methemoglobinemia due to Benzonitrile

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Abstract

Introduction: Methemoglobinemia is an uncommon condition which may be acquired by ingestion of various drugs, including dapsone and benzocaine, as well as nitrobenzene and related compounds.

Case report: A 20-years-old male presented with dyspnea following deliberate overdose of benzonitrile compound, and developed cyanosis and severe methemoglobinemia.

Discussion: Methemoglobinemia may be inherited or acquired, the latter commonly being a drug side-effect. Benzonitrile is a very rare cause of this condition, which rapidly responds to administration of methylene blue.

Introduction

Methemoglobinemia is a severe condition precipitated by oxidant stressors in the body. It occurs due to oxidation of the Fe^{2+} ion in the heme molecule of hemoglobin, leading to formation of Fe^{3+} . This dyshemoglobin has reduced ability to bind oxygen, as well as induced allosteric modification in partially oxidized hemoglobin, increasing its affinity for oxygen, and shifting the oxyhemoglobin dissociation curve to the left [1]. Hence, it reduces the oxygen-carrying capacity of blood, and also dissociation of oxygen, leading to tissue hypoxia. It may be congenital or acquired. Various drugs, commonly dapsone, and topical anaesthetic agents like benzocaine can cause this [2]. We describe a case of methemoglobinemia precipitated by deliberate ingestion of benzonitrile. The patient recovered with administration of methylene blue.

Case Report

We describe a rare case of methemoglobinemia following oral intoxication with benzonitrile. A previously healthy 20-years-old male presented to our hospital Accident and Emergency services with consumption of 250 mL of sodium benzoate with 25% benzonit and amino acids, in January 2011.

Following consumption, he complained of nausea and mild throat pain.

At presentation, his BP was 120/90 mm Hg, pulse rate was 118/minute, respiratory rate was 24/minute and saturation was 95%. During stomach wash, he desaturated to 85 % and central as well as peripheral cyanosis was noted. He was started on 100 % oxygen with reservoir bag followed by CPAP with 100% oxygen and high PEEP. However, saturation persisted at 85%. He also had deterioration of sensorium at this point in time.

Cardiovascular, respiratory and abdominal examination was within normal limits.

ABG with CO-oximetry was done which revealed Methemoglobin level of 45.3%. His arterial blood was noted to be chocolate brown in color.

His routine blood investigations were normal.

He was administered 2 mg/kg of methylene blue as an intravenous bolus. An ABG done one hour later showed reduction in Methemoglobin level to 9.4%. Another bolus dose of 1 mg/kg was administered. ABG repeated one hour later showed methemoglobin levels of 4%. ABG analysis was done every 6 hourly subsequently. After 12 hours of the

second bolus of methylene blue, his methemoglobin level rose again to 20.8%. A third bolus was administered at this point, and a methylene blue infusion was initiated to administer a total dose of 7 mg/kg over 24 hours, taking the boluses into account, hence, 1 mg/hour for 10 hours. 12 hours after the infusion was stopped, methemoglobin levels climbed to 11.6% so infusion over 10 hours was restarted. Subsequently, methemoglobin levels gradually normalized over a period of 6 days following the second infusion. He was not treated after the second infusion as the levels of methemoglobin were below 20% and he was asymptomatic.

Discussion

We report an uncommon case of benzonitrile-induced methemoglobinemia. Methemoglobinemia is a condition where methemoglobin levels in the blood exceed normal levels of 2%. It may be due to congenital causes due to absence of NADH-dependent enzyme, Cytochrome B5 reductase or cytochrome B5, inherited as autosomal recessive disorders [3]. This form is most common in Alaskan Native Americans and individuals of Inuit descent.

NADH-dependent reduction is the main system responsible for 99% of reduction of endogenous methemoglobin produced in the body. Hemoglobin M variant is also described as a congenital cause of this condition.

Acquired causes include exposure to various drugs and chemicals, as well as in sepsis, infants with severe gastroenteritis and dehydration, and sickle cell crisis. These essentially cause redox imbalances and overwhelm the normal mechanisms by which the body reduces methemoglobin.

Clinically, it results in low oxygen saturation on pulse oximetry, development of cyanosis, chocolate brown color of blood, with normal partial pressure of oxygen and calculated oxygen saturation on arterial blood gas analysis [4].

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Diagnosis is established by CO-oximetry. CO-oximetry is based on the Lambert-Beer law which measures proportion of substance based on the intensity of light that passes through them. Pulse oximetry estimates oxygen saturation by eliciting the level of reduced hemoglobin (which absorbs red light of wavelength 660 nm) and oxyhemoglobin (which absorbs light of 940 nm). Methemoglobin however absorbs at both of these wavelengths. In methemoglobin levels above 35%, the pulse oximetry oxygen saturation regresses towards 85% and plateaus at that level despite further increase in methemoglobin levels. Hence, at actual saturations above 85%, pulse oximetry underestimates the same, and at saturations below 85%, overestimates saturation.

Symptoms worsen with increasing methemoglobin levels and are worse in anemic patients.

Benzonitrile is an intermediate compound in the pharmaceutical industry. It also has antimicrobial properties. To the best of our knowledge, methemoglobinemia in association with ingestion of benzonitrile has been described in literature only once earlier so far [5].

Our patient had a waxing and waning picture with unpredictable increased in methemoglobin levels.

Such a pattern has been described in methemoglobinemia due to nitrobenzene intoxication. Nitrobenzene is known to have stores in the liver and brain from where it might be subsequently released. Whether this is also true for benzonitrile needs to be determined.

Methylene blue is the antidote of choice. This (methylthionium chloride) is an oxidant dye that channels the NADPH-reductase pathway, which is an alternate pathway in the alternate metabolism of endogenous methemoglobin. Methylene blue acts as a co-factor for this enzyme and is reduced to methylene leucoblue, which then acts as an electron donor for methemoglobin. Symptomatic methemoglobinemia, or levels above 20% are treated with 1-2 mg/kg intravenous bolus over 5 minutes. This will bring down the methemoglobin levels in 30 to 60 minutes. Additional doses of 1 mg/kg bolus can be given after rechecking levels after 1 hour. Total dose should not exceed 7mg/kg as this can lead to chest pain, dyspnea, hypotension and hemolysis with Heinz bodies [6].

Methylene blue is not useful in patients with G-6-PD deficiency where the HMP shunt is affected (this leads to the formation of NADPH in the body). Methylene blue can precipitate hemolysis in this condition. Alternate strategies with anecdotal success include hyperbaric oxygen therapy and exsanguinations-transfusion.

Our patient had increase in methemoglobin levels even after methylene blue infusion. This could be due to the excretion kinetics of sodium benzoate in humans which are not well elucidated and may have waxing and waning levels in blood. This is known for benzocaine. Because benzocaine is more lipophilic, it may continue to enter the blood stream from adipose tissue stores after methylene blue blood concentrations are no longer therapeutic.

Also, our patient was treated with injection augmentin for five days for aspiration pneumonia. This can interfere with hepatic glycine conjugation, thereby exhausting the pathway for benzoate excretion and leading to sustained increased levels in the blood.

Our patient did well and subsequently was monitored on an outpatient basis for a total duration of 10 days with daily CO-oximetry. His methemoglobin levels normalized to 2.8% by day 10.

Conclusion

Benzonitrile is a rare cause of acquired methemoglobinemia. Methylene blue can be used to treat this condition, when the patient is symptomatic or levels of methemoglobin exceed 20%. Monitoring of methemoglobin levels may be required up till 7-10 days due to possibility of increment in the methemoglobin levels.

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