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Case Report

Difficulties In Managing Methemoglobinemia

Prabhakar K[1], Anitha A[2], Rumaisa Ahmed [3*]

1. Professor, Department of General Medicine, Sri Devaraj Urs Medical Collage, Sri Devaraj Urs Academy of Higher Education and Research, Kolar.
2. Assistant Professor, Department of General Medicine, Sri Devaraj Urs Medical Collage, Sri Devaraj Urs Academy of Higher Education and Research Kolar
3. Final year postgraduate, Department of General Medicine, Sri Devaraj Urs Medical Collage,Sri Devaraj Urs Academy of Higher Education and Research Kolar

Abstract

Acute poisoning with nitrobenzene causing significant methemoglobinemia is a rare yet life-threatening emergency. A 20-year-old, female presented to Emergency in altered sensorium with a history of consumption of a bioorganic formulation. On examination she was cyanosed restless and agitated with SpO2 of 70% on room air. Blood samples drawn for ABG was chocolate brown colour on blotting paper. ABG showed metabolic acidosis with a saturation of 80%. Methylene blue 50mg in IV saline was given over 5 mins and oral ascorbic acid.

She improved slowly after the 9th day with SpO2 of 92% on room air. She was discharged on the 17th day on oral iron, ascorbic acid, and breathing exercises. Early aggressive management of severe poisoning, strongly suspected on clinical grounds may change the outcome of the patient.

Key-words: Nitrobenzene, methemoglobinemia, methylene blue, pulse oximetry.

Introduction

Acute poisoning with nitrobenzene causing significant methemoglobinemia is a rare yet life-threatening emergency. We at R.L Jalappa Hospital, kolar have frequently come across nitrobenzene poisoning. Around 5 cases were reported from our setup in 2019. Early aggressive management of severe poisoning, strongly suspected on clinical grounds may change the outcome of the patient.

Case History:

A 20-year-old, female presented to Emergency in altered sensorium with a history of consumption of vasodus, a bioorganic formulation the previous day. The patient was referred by a local practitioner who had given her a stomach wash and administered atropine. On examination she was cyanosed restless and agitated, labored respiration of 26/min, BP 80/40 mm of Hg, pulse rate 130/min, pupils were dilated, and SpO2 of 70% on room air. Her chest was clear. Oxygen improved the SpO2 to 84% only. IV fluids improved blood pressure. There was a history of pain in the abdomen and an episode of vomiting before hospitalization. Blood samples drawn for ABG was chocolate brown colour on blotting paper. ABG showed metabolic acidosis with a saturation of 80%. Ultrasound abdomen, X-ray of the chest and ECG were within normal limits. Hb was low and WBC was slightly raised. Serum creatinine and electrolytes were within the normal range. A clinical diagnosis of acute methemoglobinemia secondary to nitrobenzene was made.

***Corresponding Author**
Dr. Rumaisa Ahmed ,
Final year postgraduate,
Department of General Medicine,
Sri Devaraj Urs Medical College,
Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar-563101
Mobile No : 9482216030
E-mail: arumaisa@ymail.com
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Table 1 - Investigations of the patients (day wise)

Day	HB	TLC	PLT	BU	SC	Na	K	LDH
1st	9.5	15	61	18	0.6	143	3.8	
2nd	8.8	16.7	307					
3rd	7.9	12.6	270	11	0.5	138	3.6	217
5th	9.5	14.1	257					284
7th	6.5	14.7	240	18	0.5	135	3.6	385
10th	8.4	12.4	230					275
17th	9.4	10.8	297	21	0.5	136	3.5	

Figure 1 – Vasodus compound ingested by the patient

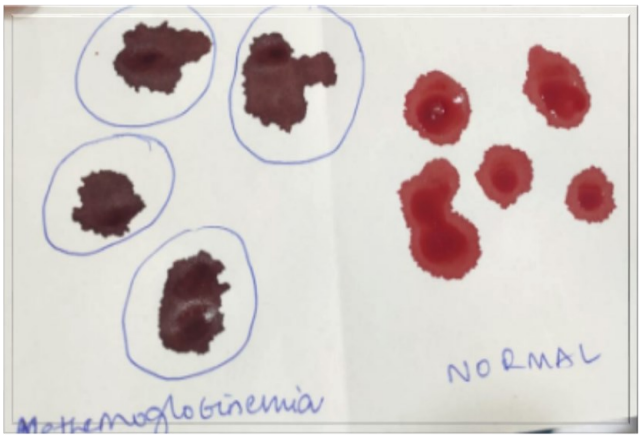

Figure 2 – Patients blood (chocolate brown) and control

Methylene blue 50mg in IV saline was given over 5 mins and oral ascorbic acid. This improved her SpO2 to 92%, which dropped after about two hours when 30 mg IV methylene blue was repeated. Two cycles of Forced alkaline diuresis were given which improved her cyanosis but there was no improvement in saturation. Urine output was maintained above 100 ml/hour with proper hydration and frusemide, maintaining a normal central venous pressure (CVP).

SpO2 was again 79% with ABG showing saturation of 94%. IV methylene blue (30 mg) improved SpO2 to 97% over the next 15 minutes, only to return to 83% in the next four hours, with a similar response to another dose. A total dose of 7mg/kg was given. She was maintaining a saturation of 90-95%. Two units of fresh blood were transfused on days 3 and 8 because of hemolysis (LFT showed hemolysis). With this waxing and waning of symptoms, intravenous methylene blue every six hours (three days) till a total dose of 7mg/kg, and oral ascorbic acid for 12 days.

Methemoglobin levels were not measured due to unavailability.

She improved slowly after the 9th day with SpO2 of 92% on room air. She was discharged on the 17th day on oral iron, ascorbic acid, and breathing exercises.

Discussion

Nitrobenzene is an oily yellowish liquid, with a bitter almonds odor. It is used in the synthesis of solvents, like paint remover. It may be due to accidental or suicidal ingestion, or the side effect of drugs like metaclopromide.[1] Accidental toxicity can occur in patients consuming well water with dangerously high levels of nitrites and nitrates. The lethal dose can range from 1 g to 10 g.[2,3] The toxic effects are due to methemoglobinemia, where the iron in the hemoglobin is oxidized from the ferrous (Fe2+) to the ferric (Fe3+) state, leading to the inability to transport oxygen and discolouring he blood.[4] Methemoglobin once formed can be reduced enzymatically via NADH dependent reaction, catalyzed by cyt b5 reductase, or an alternative pathway utilizing the NADPH dependent methemoglobin reductase system.[1]

Acute intoxication is usually asymptomatic up to the level of 10 – 15% of methemoglobin, showing the only cyanosis. Beyond 20%, headache, dyspnea, chest pain, tachypnea, and tachycardia develop. At 40 – 50% of methemoglobin, confusion, lethargy, and metabolic acidosis occurs, which can lead to coma, seizures, bradycardia, ventricular dysrhythmia, and hypertension. >70% is fatal. G6PD-deficient and anemic patients suffer more severe symptoms.[1] Leukocytosis has been reported, with relative lymphopenia.[2,3]

Other effects include hepatosplenomegaly, altered liver functions, and Heinz body hemolytic anemia. Nitrobenzene is metabolized to p-nitrophenol and aminophenol which is excreted in urine (65%) and stools (15%), after five days of ingestion. The liver, stomach, blood, and brain may also store and release it gradually.[5]

Diagnosis includes a history of chemical ingestion, the characteristic smell of bitter almonds, persisting cyanosis on oxygen therapy without the cardiopulmonary disease, low arterial oxygen saturation, with normal ABG (calculated) oxygen saturation. On shaking, blood remains dark brown in color, which suggests methemoglobinemia and this is supported by the chocolate red color of dried blood on blotting paper. Nitrobenzene compounds can be confirmed spectrophotometrically and estimated by the butanone test of Schrenk.[6] Methemoglobin levels in the blood can be estimated, and urinary presence of p-nitrophenol and p-aminophenol.[5,6]

Pulse oximetry in methemoglobinemia is misleading. Pulse oximetry shows falsely low values for oxygen saturation with low-levels of methemoglobinemia and falsely high with high-level methemoglobinemia. The reason for these inaccuracies are:

The pulse oximeter only measures the relative ab-

sorbance of light of 2 wavelengths (660 nm and 940 nm). This is to differentiate oxyhemoglobin from deoxyhemoglobin. This is converted to oxygen saturation by using calibration curves. Methemoglobin increases light absorption at both wavelengths especially more at 940 nm. It offers optical interference by falsely absorbing light to pulse oximetry.[7]

Oxygen saturation by pulse oximetry in methemoglobinemia plateaus at 85%; therefore, a patient with a methemoglobin low level and high level of having approximately the same saturation values (~85%). The severity of the cyanosis does not correlate with pulse oximetry.[7]

However, newer multiwavelength pulse oximeters have been developed that can detect methemoglobinemia with an accuracy comparable to that achievable with co-oximeters.

Recommended treatment is based on the principles of decontamination and supportive management. Methylene blue is the antidote of choice for toxic methemoglobinemia. It is an exogenous cofactor, which enhances the NADPH-dependant methemoglobin reductase system and is indicated if the methemoglobin levels are >30%.[2] It is administered intravenously at 1 – 2 mg/kg (up to 50 mg dose in adults,) over five minutes; with a repeat in one hour, if necessary. Methylene blue has an oxidant property of its own, at levels of more than 7 mg/kg hence it may cause methemoglobinemia. It is contraindicated in patients with G6PD deficiency because it can lead to severe hemolysis. Ascorbic acid is an antioxidant administered in patients with methemoglobin levels of > 30%.[8] In recent studies, N-acetylcysteine has been shown to reduce methemoglobin, but it is still not approved. Exchange transfusion is indicated in severe cases.[8] Hyperbaric oxygen is for patients with methemoglobin levels> 50% and who do not respond to standard treatment.[1]

In our case, even though the composition on the bottle did not show nitrobenzene, considering nitrobenzene as an adulterant, strong clinical suspicion changed the outcome of the patient. Repeated low dose methylene blue helped in tiding over the fluctuating symptoms due to the release of nitrobenzene from the body stores, without exceeding the maximum dose. Fresh blood transfusion improved the oxygen-carrying capacity and hemoglobin content, improving hemolysis due to methylene blue. Pulse oximetry was not relied on. Clinical picture and ABG saturation were used to monitor the patient. Adequate nutrition, urine output, and symptomatic therapy with a careful eye on kidney and liver parameters, which have been cited as late effects. Forced diuresis improved discoloration. Ascorbic acid is useful for follow-up management.[9]

Nitrobenzene is usually present in paint solvent and dyes. It can also be mixed with other insecticide or bioorganic formulations as in our case. The clinical presentation, blotting paper test and methemoglobin levels should be kept in consideration for appropriate treatment.

Conclusion

Nitrobenzene poisoning should be suspected in patients with cyanosis and low saturation that does not improve despite oxygen. The color of blood should also be kept in mind.

Pulse oximetry may be misleading hence methemoglobin levels must be estimated for accuracy and further treatment with methylene blue. Methylene blue above 7mg/kg can be an oxidant.

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