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Clinical diagnosis of acute methemoglobinemia prevents delay in treatment

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Abstract
Methhemoglobin, an altered form of hemoglobin, incapable of delivering oxygen to the tissues, can be potentially fatal if left untreated. Methemoglobinemia is an important differential diagnosis cyanosis in patients with no underlying structural heart disease. A case of acute Nitrobenzene poisoning with methemoglobinemia is presented where clinical evaluation and timely management, with repeated and judicious intravenous methylene blue helped to save a life. Secondary cycling of the drug due to the release from the stores should also be considered in the management.

Introduction

Methemoglobenemia due to acute poisoning of Nitrobenzene compound is uncommon but it is a life threatening emergency condition. Strong suspicion of the poisoning on clinical grounds with timely and aggressive management will have a major impact in the outcome of the patient

Case Report

A 27 yrs female was brought to casualty in an unconscious state with a history of ingestion of unknown poison (container not brought) with suicidal intention. She was admitted and evaluated. She was found Cyanosed with labored respiration, and her vitals were recorded as a Respiratory rate of 32/min, pulse rate 68/min, BP 90/60 mmHg,B/L pupils 3mm RTL and SpO2 of 58% on room air. On auscultation, her chest was found clear. She was intubated and ventilation with 100% oxygen improved SpO2 to only 72%. She had a history of 2 episodes of vomiting which predominantly contains food particles. To reduce further absorption of the poison, Stomach wash was given before admission in ICU. Blood samples drawn for ABG had a chocolate brown colour and showed compensated metabolic acidosis with pO2 of 466.Other investigations like ECG, X-ray chest, serum creatinine and electrolytes were within normal limits.

Liver enzymes and WBC were slightly raised. A clinical diagnosis of poison induced severe methaemoglobinaemia was made.

She was given 40 mg (5 ml) of methylene blue and 500 mg of Ascorbic acid through IV. Her SpO_2 improved to 84%, which eventually got dropped to 78% after 2 hours. Then 40 mg IV methylene blue was administered again. Intravenous Vitamin K, Dextrose, and other supportive measures were also added to the treatment.

She was transfused with single unit of fresh whole blood and this improved the SpO2 to 86%.She gained her consciousness after 12 hours with a stable BP of 110/80 and HR of 106/min.

After few hours, Her SpO_2 dropped again to 80% with ABG showing increased PaO2. IV methylene blue (40 mg) was given again and SpO_2 improved to 94% over the next 15 minutes only to return to 82% in the next three hours, with a similar response to another dose.

Patient relatives' brought the container on the next day which showed the compound ingested was Nitrobenzene 20% .She was extubated at 36 hours and maintained on a NRB mask with SpO2 of 88% and a PaO2 of 205.5. The SpO_2 dropped back to 80% in next 12 hours.

With this waxing and waning picture of symptoms, six hourly gastric lavage with charcoal, intravenous methylene blue every 12 hours (upto 3rd day) and IV ascorbic acid (500 mg per day) for five days, was prescribed.

She improved after four days and transferred to general ward from ICU with an SpO2 of 91% on room air. Psychiatric counselling was given to the patient.

She was discharged on seventh day with oral liver enzyme supplements, ascorbic acid and iron folic acid syrup.

Investigations

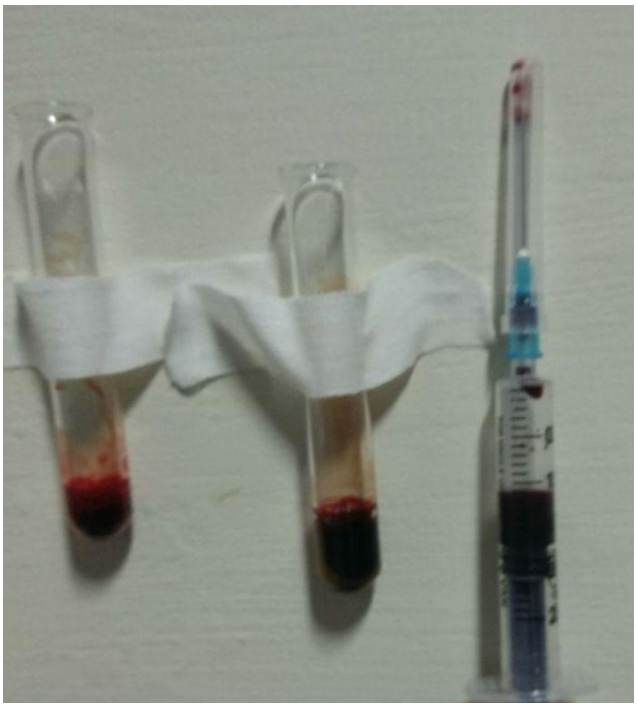
ABG Analysis

	Day 1	Day 2	Day 3	Day 4	Day 5
PH3	7.418	7.49	7.5	7.4	7.54
PO2	466.6	163.5	205.5	170	203
PCO2	19.8	19.2	26.8	31.8	27.1
HCO3	12.5	14.4	20.5	22.3	22.7
SPO2	58%	86%	91%	92%	92%

Serum Methemoglobin levels - 9.8% (Normal < 1)

	Day 1	Day 2	Day 3	Day 4
HB(g%)	12.8	12.0	14.3	
TC	4,440	2,160	6000	
Platelet count	3.38 lakhs	2.11 lakhs	2.31 lakhs	
Urea (mg/dl)	20	19	20	29
Creatinine (mg/dl)	0.9	0.9	0.8	0.8
Na + (mmol/l)	144	138	138	140
K+ (mmol/l)	3.3	3.2	3.7	3.1
Cl- (mmol/l)	10.6	92	100	105
T.Bilirubin (mg/dl)	0.9	1.0	1.2	
Direct	0.2	0.2	0.6	
SGOT	76	83	42	
SGPT	72	40	28	

Compound – Nitrobenzene 20 %



First arterial blood sample shows normal colour while other in syringe showing chocolate brown colour

Discussion

Nitrobenzene is an organic compound found as a water insoluble pale yellow oil with an smell of bitter almonds. It is commonly available in Indian rural Households due to its use in agriculture It is also used in the synthesis of dyes, explosives and in rubber industry. Cases of nitrobenzene poisoning are not new as the reports of first confirmed case came in 1886 itself[2] and subsequent fatality reports followed.[1,2] Nitrobenzene poisoning maybe accidental or suicidal, or can occur as the side effect of some drugs, like Metoclopromide.[1] Consuming well water with dangerously high levels of nitrites and nitrates is the major way of accidental poisoning.[3] A review of published reports does not provide any consistent reports regarding fatalities and dose of ingestion.[5] However, ingestion of the compound in ranges from 1 g to 10 g, has been regarded as lethal by different authors.[4,5] The main mechanism behind the toxicity of the compound is the formation of Methemoglobin,(4) a form of Hemoglobin in which the Iron molecule of heme part is in Ferric form than in Ferrous form. This reduces the affinity for Oxygen and it is called as Methemoglobinemia. This results in brownish discolouration of the blood.[3] and cyanosis on parts of the body due to decreased oxygen delivery to the cells. For reversing this condition, Methemoglobin should be reduced back to normal Hemoglobin. This can be done enzymatically either via an Adenine dinucleotide (NADH)-dependent reaction, catalysed by cytochrome b5 reductase, or an alternative pathway utilizing the nicotine adenine dinucleotide phosphate (NADPH)-dependent methemoglobin reductase system.[1]

Acute intoxication up to the level of 10 – 15% of methemoglobin usually shows no symptoms except for cyanosis. When it is more than 20%, headache, dyspnea, chest pain, tachypnea, and tachycardia will develop. When the Methemoglobin levels are about 40 – 50%, confusion, lethargy, and metabolic acidosis may occur leading to coma, seizures, bradycardia, ventricular dysrythmia, and hypertension. When the levels go beyond 70% it becomes fatal. Effects will be severe and rapid in patiens with Anemia or

G6PD- deficiency.[1,4] There is a possibility of developing Leukocytosis with relative lymphopenia.[5] along with hepatosplenomegaly, altered liver functions, and Heinz body haemolytic anaemia.[2,6] Nitrobenzene is metabolized to p-nitrophenol and aminophenol and excreted in urine, up to 65%, and in stools up to 15%, after five days of ingestion. It may get stored in liver, stomach, or brain and will be released gradually.[6]

Diagonosis of the poisoning can be made from a history of ingestion, the characteristic smell of bitter almonds, persisting cyanosis on oxygen therapy without severe cardiopulmonary disease, low arterial oxygen saturation, with normal ABG (calculated) oxygen saturation. Methaemoglobin-aemia is confirmed by presence of a Dark brown blood that fails to turn bright red on shaking, supported by the chocolate red colour of dried blood. Presence of p-nitrophenol and p-aminophenol in Urine and Presence of nitrobenzene compounds by spectophotometry and positive butanone test of Schrenk,[2] methemoglobin levels in the blood, confirms the diagnosis.[2,6,7]

Management of the poisoning is based on decontamination and symptomatic and supportive measures. The antidote of choice for the acquired (toxic) methaemoglobinaemia is Methylene blue. It is an exogenous cofactor, which greatly accelerates the NADPH dependant methemoglo-bin reductase system. Methylene blue is indicated when the methemoglobin levels are more than 30%.[4] Dose required is at 1 – 2 mg/kg (up to 50 mg dose in adults,) as a 1% solution over five minutes given intravenously; if necessary the dose can be repeated mg/kg, and therefore, may cause methaemoglobinaemia in susceptible patients . As it can lead to severe haemolysis, It is contraindicated in patients with G6PD deficiency. Ascorbic acid is the other antioxidant that can also be administered in patients when the methemoglobin levels are more than 30%.[8] N-acetylcysteine has also been shown to reduce methemoglobin, but it is not yet an approved treatment for methaemoglobinaemia.[8] In severe cases, exchange transfusion can also can be tried.[4,8] Hyperbaric oxygen is reserved only when methemoglobin level goes above > 50% or those who do not respond to standard treatment.[1]

In this case, there was fluctuating symptoms due to the release of nitrobenzene from the body stores and we used repeated low dose of methylene blue to tide over the conditition without exceeding the maximum dose. Fresh blood transfusion improved the haemoglobin content and oxygen carrying capacity improving the symptoms of the patient. Oral charcoal and purgation up to five days helped to eliminate the body stores of nitrobenzene and prevented possible secondary deterioration in the patient.[1,2] Taking care of nutrition, adequate urine output, and hepatoprotection prevented late effects like kidney and liver failure.[2,6] Forced diuresis led to a rapid fall in methemoglobin levels and improved cyanosis.[5] Ascorbic acid supplements are useful for follow-up management of methaemoglobinaemia.[9]

Conclusion

The treatment of poisoning caused by an uncommon compound is a challenge due to the vast availability of toxic chemical compounds. Also it becomes lethal when the patient does not respond properly on the preferred treatment. Clinical diagnosis should made whenever possible if the content of compound is not available thereby preventing delay in treatment. Here for acute methemoglobinemia, Methylene blue and Ascorbic acid forms the main stay of management, while fresh whole blood transfusion and hyperbaric oxygen can be tried for the symptomatic improvement. Remember Methylene blue toxicity can also worsen patient condition, so judiciary use and watchful monitoring can save the life.

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