

ACUTE NITROBENZENE POISONING: CASE FATALITY AND IMPORTANCE OF METHYLENE BLUE

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Nitrobenzene poisoning is a rare but fatal condition. It causes methaemoglobinemia (Fe³⁺) and reduces oxygen carrying capacity of red blood cells(RBC). Cyanosis develops and aerobic oxygenation is hampered. Though intravenous methylene blue is the specific antidote it is not available commonly. Here we are reporting two cases of acute nitrobenzene poisoning and the role of methylene blue to save life.

Methaemoglobinemia is a potentially fatal and rare condition. The most common cause of methaemoglobinemia is the ingestion or inhalation of oxidizing agents such as nitrates and nitrites.¹ Nitrobenzene is a poisonous agent not commonly encountered in clinical practice, which belongs to the group of aniline dyes & causes methaemoglobinemia. It is also known as nitrobenzol or oil of mirbane, is a pale yellow oily liquid with a characteristic odour like bitter almond. Two rare cases of nitrobenzene ingestion came to our emergency department, with ingestion of nitrobenzene dye on two different days. They were treated with ventilatory support and exchange transfusion, but we could save only one life.

Case Report

Case no-1:

A 20 year old girl was admitted to our hospital emergency department in the evening, with a history of ingestion of about 100ml of a dye used in printing 12 hours ago. On examination she was cyanosed, her GCS (Glasgow coma scale) was 3 (E₁V₁M₁), respiration was shallow with a respiratory rate of about 30/min. Patient was immediately intubated and ventilated with SIMV (synchronised intermittent mandatory ventilation) mode. Peripheral and central cyanosis was observed, pulse 102/min & blood pressure 110/70 mm Hg. On pulse oximetry SpO₂ was only

40%. Her blood gas analysis showed pH - 7.198, PaO₂ - 516.7 mmHg, PaCO₂ - 21.2mmHg, HCO₃ 16.4 meq/l. Serum electrolytes were within normal limits.

Haemoglobin was 11.2 gm/dl, WBC count was 11,000/dl. Serum urea, creatinine, liver function test all were within normal limits. Blood drawn for investigations was chocolate brown in colour. A filter paper test had revealed this. Acute nitrobenzene poisoning was suspected because dyes used in printing industry contains high amount of nitrobenzene.³ The absorption spectra showed wavelength peak of 258 nm matching with the pure nitrobenzene. Immediate gastric lavage was carried out. 100% O₂ was given through the ventilator. Due to non availability of intravenous methylene blue, we could not give her the specific antidote. Symptomatic treatment and vitamin C was started. Exchange transfusion was done twice with two units of packed red cells. In spite of treatment her condition deteriorated. 8 hrs after admission to the ICU she developed a cardiac arrest, from which she could not be revived.

Case no-2

A 26yr old young man, a worker in the dye industry came to our emergency department with similar complaints like in the above mentioned patient. His GCS was 3 (E₁V₁M₁) at the time of presentation. He was intubated and was ventilated on SIMV mode.

On examination peripheral and central cyanosis was observed, pulse was 94/min and blood pressure 124/74 mm Hg. On pulse oximetry SpO₂ was 80%. The blood gas analysis showed pH -7.36, PaO₂- 248.7 mmHg, PaCO₂- 31.2mmHg, HCO₃⁻ 24.4 meq/l. Serum electrolytes were within normal limits. Haemoglobin was 13.2 gm/dl, WBC count was 9,400/dl. Blood urea, serum creatinine, liver function tests were within normal limits. Blood drawn for investigation was chocolate brown in colour. A filter paper test had confirmed nitrobenzene poisoning. Treatment was similar to the previous patient, in addition he was given Methylene blue through Ryle's tube and repeated after two hours (The recommended route is intravenous only for methylene blue but due to non-availability of IV preparation we had to give it via Ryle's tube). Patient's condition improved due to methylene blue and SpO₂ increased gradually. Patient was extubated after two days and after receiving treatment in the ICU for one more day, the patient was discharged.

Discussion

Nitrobenzene is used as a solvent, for the manufacture of cellulose ethers and acetate, as a flavouring agent, and as a perfume for soap etc. Therefore it is commonly available to factory workers and can be used as a means for committing suicide. Concentration of nitrobenzene in dyes used in printing industry can be upto 80%². Hence ingestion of these dyes can cause severe nitrobenzene toxicity. Pathology behind nitrobenzene poisoning is that it oxidises Fe²⁺ of haemoglobin to Fe³⁺. Haemoglobin molecule is composed of four polypeptide chains associated with four haem groups containing an iron molecule in the reduced state or ferrous form (Fe²⁺). Haemoglobin can accept and transport O₂ only when the iron atom is in its ferrous form. When haemoglobin becomes oxidized, it is converted to the ferric state (Fe³⁺) or methaemoglobin resulting in a condition called methaemoglobinemia (MeHb) in which there is inhibition of binding and delivery of oxygen by a red blood cell.³ Methaemoglobin is not capable of transporting O₂ because it lacks the electron that is needed to form a bond with O₂. Blood normally contains approximately 1% MeHb levels.¹ The low level of MeHb is maintained by two important mechanisms. One is the hexose-monophosphate shunt pathway within the

erythrocyte by which oxidizing agents are reduced by glutathione prior to the formation of MeHb. The second mechanism against MeHb formation uses two enzymes systems: diaphorase-I (nicotinamide adenine dinucleotide methemoglobin reductase) and diaphorase -II (nicotinamide adenine dinucleotide phosphate methaemoglobin reductase). These two enzyme systems require NADH (Nicotinamide adenine dinucleotide) and NADPH (nicotinamide adenine dinucleotide phosphate) respectively to reduce MeHb to its original ferrous state. Diaphorase II quantitatively contributes only a small percentage of the reducing capacity of RBC.¹ Symptoms also depends on concentration of methaemoglobin in blood.

Methaemoglobin concentration	Symptoms
10-30%	Only cyanosis
30-50%	Dyspnoea, tachycardia, dizziness, fatigue
>50%	Lethargy and stupor
>70%	Death

Features of nitrobenzene toxicity

Central nervous system - Headache, convulsions, paraesthesia, numbness of limbs and weakness, vertigo, dizziness etc.
 Gastrointestinal-Hepatosplenomegaly, jaundice and altered liver functions
 Haematological- Haemolytic anaemia, Heinz bodies
 Cardiovascular – Tachy and brady arrhythmias
 Respiratory- Tachypnoea, cyanosis, dyspnoea
 Skin- contact dermatitis

Diagnosis

The condition is diagnosed by the history of exposure, central cyanosis with not much depressant effect on respiration. There is persistent cyanosis on oxygen therapy without improvement in observed SaO₂. There is also a difference between observed (pulse oximetry) and calculated (ABG) oxygen saturation.⁴

Treatment

It revolves mainly around gastric lavage. Stopping further exposure to the body through the skin, respiratory tract etc. O₂ therapy, and artificial ventilation if needed. Methylene blue is the antidote of choice for acquired (toxic)

methaemoglobinemia.⁵ It acts as an exogenous co-factor which greatly accelerates the NADPH dependent methaemoglobin reductase system.⁵ Methylene blue is indicated for acquired methaemoglobinemia when the level is greater than 35 to 40% and the patient has cardio-respiratory symptoms.^{5,6} The initial dose is 1 to 2 mg/kg or 0.1 to 0.2ml/kg of the 3% solution given intravenously over five minutes.⁷ Response should occur within 1hour, repeated levels of methaemoglobin can be done to assess the progress. Though in higher doses it behaves as an oxidising agent and can cause asymptomatic methaemoglobinemia⁸ ascorbic acid is often mentioned as an alternative therapy, but its reducing effect is probably too slow to have significant benefit.⁸ Exchange transfusions equal to or less than the total volume and up to greater than twice the volume have been used.⁷ Dextrose should be given⁹ because the major source of NADH in the red blood cells is the catabolism of sugar through glycolysis. Dextrose is also necessary to form NADPH through the hexose monophosphate shunt, which is necessary for methylene blue to be effective. In patients with G6PD (*Glucose-6-phosphate dehydrogenase*) deficiency methylene blue therapy may be ineffective because they may not be able to produce sufficient NADPH to reduce methaemoglobin to leukomethylene blue.¹⁰

Conclusion

Nitrobenzene poisoning is a fatal condition but it can be treated if IV methylene blue is available on time, exposure to the compound is limited, and life support is available to the patient. Many cases have been reported previously.^{1,4,7,11,12} Most of these cases are managed with I.V methylene blue and therapy started very early. Most of the patients survived.

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