

Acute Nitrobenzene Intoxication: A Report of Two Cases

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Abstract

Nitrobenzene, a pale yellow oily liquid having a bitter almonds odor used as intermediate in the synthesis of aniline dyes, and as a solvent, for the manufacture of cellulose ethers and acetate, as a flavoring agent, as a perfume for soap, and in rubber industry. Cases of self-poisoning with nitrobenzene mixed with alcohol following oral ingestion are reported. Nitrobenzene metabolites are responsible for inducing methemoglobinemia. A patient presented with unconsciousness and acute respiratory distress. Prompt dialysis saved one patient but other patient expired. The aim is to highlight the presentation and the hospital course observed in the case of nitrobenzene poisoning.

Key words: Methemoglobinemia, Nitrobenzene, Unconsciousness

INTRODUCTION

Intentional exposure is a major cause of premature mortality globally and 113914 suicides are recorded annually from India for which a variety of chemicals have been used.¹ Nitrobenzene also known as nitrobenzole or oil of mirbane is a pale yellow oily liquid with an odor of bitter almonds. Nitrobenzene is highly soluble in water readily soluble in organic solvents such as alcohol, ether and benzene, and very soluble in lipids, it serves as an intermediate in the synthesis of aniline dye, solvent, such as paint remover, a flavoring agent, a perfume for soap, and in the rubber industry.² The lethal dose is reported to range from 1 to 10 g by different studies.^{3,4} Nitrobenzene ingestion primarily causes methemoglobinemia, and this reduces oxygen carrying capacity of red blood cells and also impairs oxygen delivery to the tissues. Clues for diagnosis, includes a history of chemical ingestion, characteristics smell of bitter almonds, persistent cyanosis on oxygen therapy without severe cardiopulmonary disease, and low

arterial oxygen saturation with normal arterial blood gas analysis. Acute poisoning with nitrobenzene has resulted in methemoglobinemia, cyanosis, anemia, and neurological effects including headache, nausea, vertigo, confusion, unconsciousness, apnea, coma, and death.⁵ Early and aggressive management of severe poisoning, strongly suspected on clinical grounds may change the outcome of a patient. Here, we are reporting two such cases.

CASE REPORT

Case 1

A 17-year-old unconscious male presented to emergency with cyanosis and a grayish-brown hue, labored respiration of 30/min, blood pressure (BP) 60 mm Hg systolic, pulse rate of 150/min, pupils with normal size sluggish reaction, and SPO₂ of 60% on air. His chest was clear. The patient was immediately placed on 100% O₂ by high flow mask. Dopamine support was started at ionotropic dose. There was a history of ingestion of shoe paint remover solvent followed by severe pain in abdomen, nausea, vomiting, and dizziness, after which he was brought to hospital. His arterial blood sample was found to be chocolate brown in color which was suspected to be due to methemoglobinemia. His ABG was suggestive of metabolic acidosis with pH 7.12, PaO₂ 130 mm Hg, PaCO₂ 44 mm Hg, and HCO₃ 13.3 meq/L. Gastric lavage was done via naso-gastric

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tube with sodium bicarbonate, followed by administration of activated charcoal (1 g/kg of 20% suspension) and started with intravenous (IV) fluids. His SPO₂ became 86% but he developed respiratory distress. BP was 90/60 mm Hg on inotropic support. X-ray chest and Electrocardiograms (ECG) were within normal limits. Total leukocyte count (TLC) was 14000/dl with serum bilirubin 1.8 mg/dl (conjugated 1.0, unconjugated 0.80), serum glutamic oxaloacetic transaminase (SGOT) 23, and serum glutamic pyruvic transaminase (SGPT) 21. Urine was dark colored. Serum creatinine and electrolytes were within normal limits. A clinical diagnosis of acute nitrobenzene poisoning with severe methemoglobinemia was made.

Hemodialysis was done and slow IV infusion of ascorbic acid 1 g in 5% dextrose was given thrice a day. After 2 h of dialysis, patient became stable with SPO₂ of 92% and BP of 110/70 mm Hg. His sensorium improved and he became fully conscious after 4 h of dialysis. Gradually, his inotropic support was tapered, and he was discharged on the 5th day.

Case 2

A 21-year-old male was brought to the emergency department with alleged ingestion of some unknown chemical substance. He worked in a printing press. On admission, he was in an unconscious state, not responding to verbal commands and pain. There was history of an episode of vomiting. On examination, the pupils were found dilated, reacting sluggishly to light. Heart rate was 63/min, BP - 76/34 mm Hg, SPO₂ 70%, respiratory rate was 38/min. On examination, cyanosis was present, with marked bluish discoloration of nail bed, fingertips and lower palpebral conjunctiva. Chest auscultation revealed bilateral crepitations. Abdomen was found soft to palpation. The patient was immediately intubated. Inotropic support in the form of dopamine was given. Gastric lavage was done and 100% oxygen was begun. The blood sample withdrawn for investigations revealed severe brownish discoloration with compensated metabolic acidosis. ECG recorded at the time of admission and thereafter was normal with normal chest X-ray. Blood investigation revealed leucocytosis, elevated liver enzymes with mildly deranged renal profile. The urine was dark brown colored. The hemoglobin (Hb) was 6.6 g/dl with TLC 12,600/mm³, blood sugar (mg/dl) 121, blood urea (mg/dl) 56, SGOT (U/L) 159, SGPT (U/L) 118, and serum creatinine (mg/dl) 2.1. He was given IV fluids, antibiotics, pantoprazole, and ondansetron. One unit of whole blood was transfused. A clinical diagnosis of acute severe methemoglobinemia of unknown origin was made. From the information provided by the attendants it was derived that the substance consumed was most likely nitrobenzene solution which was used in the printing process as a reducing agent. The patient was put on conservative treatment and hemodialysis was done for 4 h.

The patient failed to respond to treatment administered and expired the next day.

DISCUSSION

Acute poisonings due to ingestion of nitrobenzene present in consumer products have occurred frequently in the past and are accidental or suicidal.⁶ The first report of nitrobenzene poisoning came in 1886⁷ and subsequent fatality reports followed.^{6,7}

The symptoms which were present were non-specific except for cyanosis which is a typical finding in cases of nitrobenzene poisoning, as methemoglobinemia commonly occurs. This happens when nitrobenzene oxidizes ferrous ion of Hb to ferric state (Fe³⁺), resulting in decreased binding and delivery of oxygen by red blood cells.⁸

Acute intoxication is usually asymptomatic up to the level of 10-15% of methemoglobinemia, showing only cyanosis. Beyond 20% headache, dyspnea, chest pain, tachypnea, and tachycardia develop. At 40-50%, confusion, lethargy, and metabolic acidosis occur leading to coma, seizure, bradycardia, and ventricular arrhythmia. Anemic and G6PD deficient patients suffer more severe symptoms.^{3,4}

Nitrobenzene is metabolized to p-nitrophenol and aminophenol and excreted in urine up to 65% and in stools up to 15% after 5 days of ingestion. Liver, stomach, brain, and blood may act as stores and release it gradually.⁸

Symptoms of nitrobenzene ingestion include burning sensation in the mouth, numbness of the tongue, salivation, nausea, vomiting, diarrhea, giddiness, throbbing headache, marked cyanosis, cold and moist skin, weak and rapid pulse, hurried breathing, drowsiness, and coma. The blood is likely to be chocolate-colored due to the presence of methemoglobin. The pupils get constricted at first, and then dilated. Urine becomes dark colored. Convulsions may occur before death. Gastrointestinal toxicity may result in hepatosplenomegaly, jaundice, and altered liver functions. Hematological toxicity may show methemoglobinemia, hemolytic anemia, and Heinz bodies.⁹⁻¹¹

The fatal dose of nitrobenzene is said to be about fifteen drops, and the MAC in air is about 1 ppm. Death usually occurs within 6-7 h of ingestion.¹⁰

Chemically induced methemoglobinemia is a life-threatening condition which requires immediate and definitive management. Methemoglobinemia management can be classified into five categories: (1) Reducing toxin's systemic absorption by induction of emesis with ipecac syrup/salt water and facilitating removal of toxin from gastrointestinal

tract by gastric lavage, activated charcoal, and a purgative, (2) reduction of methemoglobin to Hb via reducing agents, (3) treatment of the “functional anemia” (hypoxic state) with hyperbaric oxygen, (4) extracorporeal removal of the chemical, and (5) replacement of methemoglobin with a functional oxygen-carrying pigment.¹²

The definitive treatment of methemoglobinemia is the use of the reducing agent, methylene blue whose action is dependent on production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) by the hexose phosphate shunt and the activity of the enzyme, NADPH-methemoglobin reductase. NADPH is necessary for the reduction of methyleneblue to leukomethylene blue, which is responsible for the reduction of methemoglobin into hemoglobin.^{11,13} Role of ascorbic acid in reducing methemoglobinemia is controversial as its action is slow and offers little advantage over normal endogenous reduction of methemoglobin. Methylene blue is available as 1% 10 ml vial and for the initial management of methemoglobinemia recommended dose is 1-2 mg/kg to a maximum of 5-7 mg/kg/day. As maximal response to methylene blue usually occurs within 30-60 min; therefore, methemoglobin levels should be monitored and repeat doses of methylene blue should be spaced at least 1 h apart and after evaluating the response to the last dose. G6PD deficiency should be considered if a patient has a negligible initial response to a therapeutic dose of methylene blue.¹⁴ Methemoglobin levels should be continuously monitored as nitrobenzene has the potential for continued methemoglobin production.^{12,15} N-acetylcysteine has a controversial role in reducing methemoglobin, so its use not yet approved.¹⁶ Exchange transfusion is indicated in severe cases.¹⁷ Hyperbaric oxygen is reserved for patients who have a methemoglobin level >50% and or those who do not respond to standard treatment.¹¹

The patients were unconscious with respiratory distress and hypotension. Due to non-availability of methylene blue specific treatment was not possible at our setup. The patients were treated with supportive therapy. Both patients were posted for dialysis as a desperate measure. The first patient improved, but the second patient failed to respond to the treatment and expired.

CONCLUSION

Acute methemoglobinemia is usually associated with high mortality. Methylene blue and ascorbic acid are treatment

of choice. Blood exchange transfusion and hyperbaric oxygen therapy are usually reserved for patients who are resistant to standard treatment. Forced diuresis lead to a rapid fall in methemoglobinemia and improve outcome.³

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