Case Report
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Successful Treatment of Nitrobenzene Poisoning with Oral Methylene Blue and Ascorbic Acid in a Resource Limited Setting

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Abstract:

Nitrobenzene as a weedicide is rarely being consumed as a means of suicide. Its combination with an organophosphorus compound poses additional dilemma in the diagnosis and treatment if the culprit poisons can not be identified accurately. The matter gets complicated in a resource poor setting in a developing country where even ideal medications are not available. A 55 year old male with a suicidal consumption of a cocktail of unknown substance was saved by alert diagnosis of methemoglobinemia followed by treatment with the laboratory preparation of locally available oral methylene blue and high dose oral ascorbic acid. The unnecessary need for the mechanical ventilation was judiciously avoided even in the setting of a persistently low pulse oximetry readings.

Keywords: ascorbic acid , methemoglobinemia, methylene blue, nitrobenzene

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A 20% emulsion of nitrobenzene is widely used as a weedicide in India. The fatal dose of nitrobenzene ranges from 4.3 to 11.0 grams based on urinary P-nitrophenol levels [1]. Manifestations range from cyanosis, headache, tachypnea, seizures, metabolic acidosis, coma and death due to respiratory failure. Co-ingestion of nitrobenzene with an organophosphorus compound delays the diagnosis of the former by masking the less stringent bitter almond smell and delaying the development of cyanosis, altered sensorium, features of hemolytic anemia etc. by several days due to its slow release and systemic redistribution from adipose tissue and gastrointestinal tract. Here we report a case of suicidal poisoning by a cocktail of nitrobenzene and an organophosphorus compound which pose a unique challenge in diagnosis and treatment in the setting of unavailability of injectable methylene blue in most of the secondary and tertiary care health centers throughout India.

Case Report

A 55 year old farmer was admitted with a history of consumption of unknown substance 12 hours prior to the arrival at the emergency room. He was referred from the primary health centre as a case of suspected organophosphorus poisoning. He was adequately atropinised but was referred in view of persistently low SpO_2. Glasgow Coma Scale (GCS) at the time of admission

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was E_2 V_2 M_4. Blood pressure, pulse, respiratory rate were in normal range except for a pulse oximetry reading of 82%. General examination was normal. Cardiovascular, respiratory and neurological examination did not reveal any abnormality. Atropine, antibiotics, supplemental oxygen was continued and samples were sent for routine examinations. All laboratory parameters were normal except for a mild neutrophilic leukocytosis on peripheral smear. However, inspite of continuous high flow oxygen therapy, SpO_2 fluctuated at 78 % to 82%. Sensorium did not improve and the patient developed persistent nausea and vomiting, tachypnea with a respiratory rate of 30/min and a subtle cyanosis [figure 1]. One episode of generalized tonic clonic seizure occurred on the 2nd day of admission and the patient was put on IV Phenytoin therapy. On the day 3 Arterial Blood Gas (ABG) test was planned which showed a pH of 7.49, PaO_2 of 91 mm Hg, pCO_2 of 37 mm Hg, HCO_3 of 27.3 mmol/L and an oxygen saturation of 98%. The arterial blood sample was chocolate brown in color that failed to turn red even with vigorous shaking. In view of the characteristic color of the arterial blood and the discrepancy of the oxygen saturation on pulse oximeter and ABG readings, the possibility of methemoglobinemia was entertained and samples were sent for estimation of methemoglobin levels which came out to be 59.7% and carboxyhemoglobin level was 0%. Repeat CBC on day 3 also showed features suggestive of hemolysis with target cells and an uncorrected reticulocyte count of 12%. Serum lactate dehydrogenase (LDH) levels were raised at 3100 IU/L.

Figure 1. Subtle cyanosis of the hand



A provisional diagnosis of methemoglobinemia was made on day 3 which was substantiated later when patient's attendants brought empty bottle of 20% nitrobenzene compound (ALLWIN GOLD). Samples were sent for G6PD activity prior to starting of methylene blue (MB) therapy which came out to be normal. As injectable MB was not available in our setting and in view of rapidly deteriorating clinical status of the patient, oral MB was administered by constituting a sterile 1% solution from locally available laboratory grade MB powder along with high doses of oral ascorbic acid 1000 mg every 6 hourly. Treatment was continued for 4 days. At the end of 2nd day of treatment with oral MB and ascorbic acid, cyanosis and sensorium started to improve and at the end of 4th day patient was significantly better with no cyanosis and a GCS of E_4 V_5 M_6 and a pulse oximetry reading of 92%. Methemoglobin levels were repeated which came to be at 11%. Repeat ABG was normal. Oral MB therapy was stopped on day 4 but oral vitamin C was continued for another 4 days and discharged. At the time of discharge repeat methemoglobin levels were 3.4 %. Patient was reviewed after 7 days and was completely asymptomatic.

Discussion

Nitrobenzene being an oxidizing nitrite compound rapidly leads to methemoglobinemia, a fatal condition in which ferrous (Fe^{2+}) iron gets oxidized to ferric (Fe^{3+}) form resulting in decreased oxygen carrying capacity and decreased delivery of oxygen to tissues shifting the O_2-Hb dissociation curve to left [2]. Cyanosis developing in such a setting is usually unresponsive to high flow oxygen therapy.

Methemoglobin levels in health and physiological states never exceed 2-3% [3]. Asymptomatic cyanosis develop at methemoglobin levels >10%. Symptoms of acute intoxication such as headache, lethargy, tachypnea, tachycardia occur at levels of 20-50 %. Levels above 50% is associated with confusion, seizures, arrhythmias and metabolic acidosis. Beyond 70% death generally occurs due to cardiovascular collapse and or respiratory failure [4].

Physiological levels of methemoglobin are kept in check by hexose monophosphate (HMP) shunt pathway in the erythrocytes by glutathione which reduces the exogenous oxidizing agents prior to the formation of methemoglobin. A second mechanism utilizes the enzyme systems viz. Diaphorase – I and II which inturn uses NADH and NADPH enzymes to reduce ferric (Fe^{3+}) iron of methemoglobin back to ferrous (Fe^{2+}) form [5].

The cytochrome –b5 MHbreductase plays the most vital role in reduction of methemoglobin [6].

Two forms of methemoglobinemia are described – Congenital (Diaphorase I deficiency, Hg H and Hg M variants, G6PD deficiency etc.) and Acquired [2]. The characteristic smell of bitter almonds, refractory cyanosis to high flow oxygen therapy, persistently low SpO_2 with normal ABG oxygen saturation levels, failure of the chocolate brown color of arterial blood to turn into bright red on vigorous shaking are various bedside indicators to consider methemoglobinemia as a differential diagnosis. Co-oximeter is often the preferred method to analyze the true oxygen content of blood when abnormal hemoglobin is present [7].

IV methylene blue as the antidote of choice scores over other available alternative treatments like ascorbic acid, n-acetyl cysteine etc. Oral administration of methylene blue is subjected to extreme first pass metabolism which limits the attainment of peak concentration over a short period of time [8]. IV methylene blue is administered as a 1% solution at 1-2 mg/kg over 5 minutes and repeated in an hour if necessary. It acts as a electron donor and rapidly reduces methemoglobin to ferrous (Fe^{2+}) state via NADPH- metHbreductase system. Methylene blue at cumulative doses of > 7 mg/kg behaves paradoxically as an oxidant and exacerbate methemoglobinemia [9]. Methylene blue is contraindicated in G6PD deficient individuals as it causes severe hemolysis.

Ascorbic acid (vitamin C) acts as a free radical scavenger and reduces NAD^-. It is used as a single agent in moderate doses of 300 – 1000 mg/day orally in divided doses in patients with symptomatic methemoglobinemia in whom methylene blue is contraindicated and in high doses of 10 grams IV 6 hourly for treatment of symptomatic methemoglobinemia in patients without renal insufficiency where methylene blue is not available [10]. There are no randomized controlled trials comparing methylene blue and vitamin c, but studies suggest that a single dose of methylene blue reduces methemoglobin to non-toxic levels (<10%) within 1 hour as compared to more than 24 hours with vitamin C and hence the later is a poor alternative in emergency situations [11].

Cimetidine used as a selective inhibitor of n-hydroxylation have some role in treatment of dapsone-induced methemoglobinemia [12]. N-acetyl cysteine was shown to have no effect in decreasing methemoglobin levels [13]. Exchange transfusion and hyperbaric oxygen therapy is reserved for patients resistant to standard therapies.

Our patient was initially treated for organophosphorus poisoning and later found to be a case of co-poisoning with a nitrobenzene compound. The onset of signs and symptoms suggestive of methemoglobinemia were delayed by 3 days. This peculiarity may be explained by the slow release of the substance from adipose tissue and redistribution from gastrointestinal and other body stores and also by masking of the obvious symptoms by the more obvious organophosphorus poisoning. To complicate the scenario, non-availability of injectable methylene blue and vitamin C in our setup prompted us to use oral methylene blue solution and high doses of oral vitamin C which saved the life of our patient although the treatment course was prolonged for a few extra days.

Conclusion

Uncommon poisoning of a nitrobenzene compound in a resource limited setting often creates a challenging situation in accurate diagnosis and appropriate management. Non-availability of injectable methylene blue and or vitamin C should not be a hindrance for initiating treatment and rather the use of locally available methylene blue powder or solution can often be life-saving. The treatment course albeit a bit prolonged is nevertheless insignificant.

Conflict of Interest

None Declared

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