CASE REPORT

Case of methaemoglobinaemia caused by tree oils and kerosene

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SUMMARY

We report a case of a young man who allegedly consumed 100 mL of an indigenous pesticide which is used for the killing of rats in households in India. The constituents were azadirachtin oil (40%), tea oil (15%), pine oil (25%) and kerosene oil (20%). He presented to us with shortness of breath and altered sensorium and was found to have fMetHb (fraction of methaemoglobin) level of 80%, which has been postulated to have a fatal outcome. He responded to a low dose of methylene blue along with intravenous vitamin C and the level of fMetHb came down to 20% within 1 hour. His sensorium improved markedly with a decrease in fMetHb to non-toxic levels and he was discharged 5 days after admission. A literature review pertaining to these constituents individually or in combination causing methaemoglobinaemia is discussed in the context of this case.

BACKGROUND

There is a big market of unregulated pesticides in India. The main constituent of the poison consumed by our patient was azadirachtin oil, which is a derivative of neem oil. Neem oil has been used in traditional as well as contemporary times in India as a biopesticide to repel a wide variety of pests like moths, caterpillars, termites, and so on. The constituents of this pesticide have never been reported to cause methaemoglobinaemia either in isolation or when consumed with other agents described subsequently. This is the first reported case of methaemoglobinaemia caused by this cocktail of oils. Despite the fact that the level of fMetHb (fraction of methaemoglobin) $\geq 70\%$ is fatal, our patient survived.

CASE PRESENTATION

A 28-year-old man who lived alone and was working as a cleaner in a restaurant was found by his landlord in altered sensorium who then reported this to the police. Subsequently, he was brought to the emergency department of the All India Institute of Medical Sciences, New Delhi, by the police. A 100 mL empty bottle named 'Nimolin' whose constituents were inscribed on the bottle (azadirachtin oil (40%), tea oil (15%), pine oil (25%) and kerosene oil (20%)) had been found by the side of the patient at his home. On examination, the patient was found to be in altered sensorium with Glasgow coma score of E3V1M5 with cyanosis and tachypnoea. On room air, his SpO₂ by pulse

oximetry was 80%. He was subsequently intubated, put on mechanical ventilation and shifted to the intensive care unit (ICU) for monitoring. In view of disproportionate hypoxia as suggested by the low SpO₂ with cyanosis and circumstantial evidence suggesting poisoning, a suspicion of methaemoglobinaemia was made and an arterial blood sample was drawn. The arterial blood was chocolate brown in colour with fMetHb levels of 80%. His partial arterial oxygen pressure (PaO₂) was 300 mm Hg on a fraction of inspired oxygen (FiO₂) of 100% while his SaO₂ (functional saturation of arterial haemoglobin) as measured by co-oximetry was 100%. In view of raised fMetHb levels and disparity between pulse oximetry and co-oximetry, a diagnosis of methaemoglobinaemia was made.

TREATMENT

Keeping the possible fatal consequences of the condition in case active intervention was delayed, informed consent was taken from the attendant of the patient for use of methylene blue and intravenous vitamin C without waiting for glucose-6-phosphate dehydrogenase (G6PD) level. Only 10 mg of methylene blue could be arranged, which was given along with 8 g of intravenous vitamin C. After 1 hour of giving this therapy, the cyanosis decreased, sensorium improved and fMetHb levels fell to 20%. He was subsequently extubated after about 1 hour and resting SpO₂ while breathing ambient air was 85%. He was shifted from the ICU to the ward within a day and was started on oral vitamin C tablets 500 mg three times daily. His fMetHb levels were followed up by venous blood gas analysis as shown in figure 1. On the second day, there was an increase in fMetHb to 24.6% after which intravenous vitamin C was restarted. The next day, fMetHb levels came to $<10\%$; intravenous therapy was discontinued and oral vitamin C was restarted.

OUTCOME AND FOLLOW-UP

The patient underwent a formal psychiatric evaluation and therapeutic planning for his alleged suicide attempt and was discharged in a stable condition after 5 days of admission. He is currently under follow-up in psychiatry outpatient department.

DISCUSSION

Under normal physiological conditions, human blood contains $\leq 2\%$ haemoglobin in the form of MetHb. Methaemoglobinaemia can be either congenital or acquired. Congenital methaemoglobinaemia is due

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Figure 1 fMetHb (fraction of methaemoglobin) levels in blood. iv, intravenous.

to deficiency of cytochrome-b5 reductase in red blood cell or in other tissues.¹² In usual circumstances, the endogenous reducing agents present in blood are able to keep the fraction of MetHb to less than 2%. In a situation of an excess of oxidation potential, these reducing agents are easily overwhelmed (100–1000 times), especially so in those with G6PD deficiency.³ There is a long list of the potential causes of acquired methaemoglobinaemia which include paraquat, naphthalene, burning smoke of woods and plastics, industrial compounds like nitrates and nitrites, local anaesthetics, sulfonamides, and so on.⁴

Methaemoglobin, carboxyhaemoglobin and sulphaemoglobin are types of haemoglobin which do not bind with oxygen. The oxidised ferric ion (Fe+3) in methaemoglobin cannot bind oxygen and in addition, also leads to an allosteric change in the haem portion of oxidised haemoglobin which causes a left shift in the O₂-Hb dissociation curve, ultimately causing decreased oxygen delivery to tissues.⁵ Thus, hypoxia occurs due to both decreased oxygen binding to haemoglobin as well as impaired release at the tissue level.

Clinical manifestations reflect reduced oxygen carrying capacity of blood. Neurological (dizziness, headache, anxiety, seizures) and cardiac (palpitations, syncope) symptoms are usually evident after levels of fMetHb have reached 20%–30%. Levels more than 70% are usually fatal.⁴

Low oxygen saturation out of proportion to the haemodynamic profile and clinical examination should point towards a possibility of methaemoglobinaemia. The use of only two wavelengths (600 and 640nm) limits the discriminatory capacity of the pulse oximeter to differentiate between oxyhaemoglobin (O₂Hb) and reduced haemoglobin (HHb).

Co-oximetry, which uses multiple wavelengths, works on the principle of Beer-Lambert law and is considered the gold standard for diagnosis of methaemoglobinaemia.^{6,7} There are important limitations of co-oximetry which must be kept in mind. Since the absorbance characteristics of methylene blue are similar to methaemoglobin, it can be interpreted by the co-oximeter as methaemoglobin and can overestimate its concentration

Figure 2 Two-dimensional structure of azadirachtin.

after treatment with methylene blue.⁸ Therefore, methaemoglobin detected by the co-oximeter should be confirmed by the specific Evelyn-Malloy method,⁹ especially after treatment with methylene blue. This method could not be used in our case due to non-availability of the same.

Azadirachtin oil is derived from neem seed (*Azadirachta indica*). It contains a highly oxidised tetranortriterpenoid ingredient which has a lot of oxygen bearing functional groups as seen in figure 2.^{10,11} Robert Krieger in his book '*Handbook of Pesticide Toxicology*' describes 13 poisoning cases due to neem seed, out of which two were fatal. He writes 'five to ten ml of the oil given orally to children against minor ailments caused vomiting, drowsiness, tachypnoea with acidotic respiration, and polymorphonuclear leukocytosis, and encephalopathy developed within hours of ingestion. Seizures associated with coma, developed in some cases. Autopsy in these cases demonstrated pronounced fatty acid infiltration of the liver and proximal renal tubules, with mitochondrial damage, and cerebral edema changes consistent with Reye's syndrome'.¹² Degeneration of terpenoids in stored tea oil¹³ has been shown to cause contact dermatitis but never methaemoglobinaemia.

Pine oil¹⁴ is a phenolic disinfectant and phenol has been implicated as a cause of acquired methaemoglobinaemia.⁴ Therefore, it is possible that pine oil might have been the culprit in our case. Kerosene has been mostly implicated in accidental poisoning and causes aspiration pneumonia in children.¹⁵ There is no literature available in which methaemoglobinaemia has been reported due to kerosene poisoning.

Since there were no signs or symptoms suggestive of kerosene poisoning, the two agents that could have possibly led to methaemoglobinaemia are azadirachtin oil (present in the maximum concentration and its chemical structure) or pine oil (due to its phenol content).

There are no clinical trials comparing intravenous methylene blue with intravenous vitamin C in the management of methaemoglobinaemia. It is recommended that methylene blue should be used since a single dose is able to reduce levels of methaemoglobin to a much larger extent than multiple doses

of intravenous vitamin C. Treatment is usually recommended if the patient is symptomatic or fMetHb levels are above 30%.⁴ Intravenous vitamin C should be used if methylene blue is not available.¹⁶ Methylene blue is included in the 17th WHO model list of essential medicines 2015.¹⁷ In our case, we used 10 mg of methylene blue (due to limited availability) along with intravenous vitamin C. Subsequently, G6PD level was also done and was found to be normal in this patient.

We had no clue regarding the half-life of the contents of the poison, therefore, when the level of fMetHb increased again on the second day, intravenous vitamin C was reintroduced. The fact that there was a rapid decline in the fMetHb levels over the next 24 hours, it is our conjecture that the initial response on day 1 might as well be because of intravenous vitamin C since the dose of methylene blue used was minuscule (10 mg, as opposed to recommended dose of 1–2 mg/kg).

Despite the extensive review, we did not come across any instance where any of the constituents of the consumed substance, either in combination or individually, has caused methaemoglobinemia. Though neem oil is commonly used as a disinfectant in Indian household and industry, its toxicity on ingestion has never been described. To the best of our knowledge, this is the first time that azadirachtin oil, tea oil and pine oil with kerosene combination have been found to cause methaemoglobinemia.

This case highlights the fact that there is a wide variety of unregulated pesticides available in the Indian market and their human toxic side effects are largely unknown. With the increase in man–society conflict, the intentional or accidental consumption of these agents can lead to life-threatening consequences. A thorough clinical examination with proper use and interpretation of laboratory parameters coupled with sound knowledge of

treatment modalities can prove pivotal for the better outcome of these patients.

Contributors All the four authors contributed to the clinical care of the patient. KG: junior resident in charge. MJ: senior resident in charge. RSJ: assistant professor in charge. RS: professor in charge. All the four authors contributed to the writing of the paper. KG: conceptualised and wrote the first draft. MJ and RSJ: contributed to revisions. RS: contributed to conceptual design, revisions and finalisation of paper.

Competing interests None declared.

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Learning points

- As more chemical agents are being promoted as insecticides/pesticides, up to now unknown agent can cause methaemoglobinemia.
- The disparity between pulse oximetry and co-oximetry should raise suspicion of methaemoglobinemia.
- Intravenous vitamin C can be given in the case of non-availability of methylene blue.
- A close watch should be kept for haemolysis as both intravenous vitamin C and methylene blue can cause the same in G6PD-deficient individuals.

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