Reminder of important clinical lesson

Acute methaemoglobinaemia after massive nitrobenzene ingestion

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Abstract

Flower-N is a flowering stimulant composition with 22% nitrobenzene. The main systemic effect associated with human exposure to nitrobenzene is methaemoglobinaemia. A 25-year-old female presented after 3 hours following ingestion of 100 ml of 22% Nitrobenzene (Flower-N). Her initial methaemoglobin (MetHb) was 81%; this responded to methylene blue. However, she developed recurrent methaemoglobinaemia on days 3 and 5 with haemolytic anaemia. The treatments that were provided were repeated methylene blue treatment and exchange transfusion. Nitrobenzene ingestion is a known cause of methaemoglobinaemia and haemolytic anaemia. The recurrence suggests a long half-life. The recurrent MetHb has clinical implications as patients may require repeated treatment. Massive nitrobenzene ingestion can cause haemolysis and recurrent methaemoglobinaemia.

BACKGROUND

Flower-N (Vivid Pesticides, New Delhi) is a flowering stimulant composition with nitrobenzene for agricultural and horticultural flowering crops comprising 22% nitrobenzene as an active ingredient with a natural/synthetic/ionic (or) non-ionic chemical surfactant and a petroleum (or) non-petroleum solvent base. Nitrobenzene toxicity has been well-established in case reports and exposure in man or experimental animals is most often associated with methaemoglobinaemia. Although these reports have been published, there are no previous reports of recurrent methaemoglobinaemia following nitrobenzene ingestion.

CASE PRESENTATION

A 25-year-old previously healthy woman was transferred from a local hospital to the intensive care unit 3 hours after consumption of a whole bottle (100 ml) of Flower-N. She was restless, combative, with obvious cyanosis (fig 1) and a Glasgow Coma Scale (GCS) of 10. There was no jaundice. Pulse was 133 beats/min and blood pressure 100/70 mmHg. Pupils were 3 mm bilaterally with normal reaction. Her respiratory rate was 16 per minute and the rest of her respiratory examination was normal. Bedside pulse oximetry showed saturation of approximately 84% while she was on 100% oxygen. There were no other significant findings on physical examination.

INVESTIGATIONS

The patient’s blood was noted to be "chocolate brown" and subsequent arterial blood gas showed a pH 7.447, PaO₂ 61.6, PaCO₂ 28.7, HCO₃⁻ 20, O₂Sa 92.7% and a methaemoglobin (MetHb) level of 81% (quantitative MetHb level was determined by a method described by Evelyn and Malloy using a visible spectrophotometer²). Initial laboratory findings revealed a haemoglobin level of 14.2 g/dl, white blood count of 14.2×10⁹/L and showed polymorphonuclear leucocytosis with normal platelet counts and total bilirubin. She had mild increase in transaminases (<2-fold). Serum electrolyte levels, urine, electrocardiogram and chest x ray were within normal limits.
TREATMENT

She was administered 200 ml of normal saline initially and maintained thereafter with 30 ml/hour. A bolus dose intravenously of 200 mg hydrocortisone and 750 mg cefuroxime (twice a day) was given. She was further administered 100 mg (2 mg/kg) of intravenous methylene blue (MB) infusion over 15 min; 45 min later, she became more lucid and less agitated. Her MetHb level at this point was 31%. A further dose of MB (50 mg) was given and 1 hour following the second dose her MetHb level was 11.9% (fig 2). At this point she regained full consciousness and was able to give details about the incident, positively identifying Flower-N as the ingested substance and confirming that she had drunk the whole bottle (100 ml), which she had bought with suicidal intent. The relatives subsequently presented the intact label a few hours later.

During the subsequent days she had no complaints, but on day 3 she was noted to be more cyanosed and complained of dizziness and general weakness. Blood taken for MetHb revealed a level of 39.3% and subsequently another dose of MB (50 mg) was given and her MetHb dropped to 22.7% an hour later.

On day 4, she had significant improvement of her condition and on day 5 her MetHb levels were 28.9%; although she had no complaints, subsequent laboratory investigation revealed a white blood cell count of 20 400 cells/mm$^3$ with neutrophilia. Haemoglobin had fallen to 10 g/dL, with a mean cell haemoglobin concentration of 31.8 g/L, smear showing normochromic, normocytic red blood cells that demonstrated polychromasia and bite cells consistent with haemolysis. In view of the persistently high MetHb levels and insufficient response following repeated doses of MB, exchange transfuse to 30% blood replacement.

OUTCOME AND FOLLOW-UP

Repeat daily MetHb levels thereafter showed a progressive decline (fig 2) and she remained asymptomatic until discharged on day 11. Follow-up was planned to assess glucose-6-phosphate dehydrogenase levels 3 months after discharge.

DISCUSSION

Acute ingestions of nitrobenzene leading to methaemoglobinaemia is well-known.\textsuperscript{3-5,10-11} Nitrobenzene metabolism in animal models are phase II in nature either via oxidation or reduction.\textsuperscript{12} Oxidation products of nitrobenzene include o-, m-, and p-nitrophenol; reduction products of nitrobenzene include nitrosobenzene, phenylhydroxylamine and aniline.\textsuperscript{13} The interconversion between the parent compound nitrobenzene and its primary metabolites (nitrosobenzene, phenylhydroxylamine and aniline) may lead to oxidation of the haemoglobin prosthetic group to the ferric state. Subsequently, these biochemical effects lead to critical redox and macromolecular binding imbalances progressing to anaemia due to haemolysis and depletion of the oxygen-carrying capacity of red blood cells.\textsuperscript{14}

There are no previous reports of recurrent methaemoglobinaemia following nitrobenzene exposure. Our patient’s ingestion was large and, in this situation, it is likely that the metabolism of parent compound and active metabolites was saturated leading to prolonged exposure to the active metabolite and cycling of the reductive products of nitrobenzene causing persistent oxidative stress. This clinical implication is a requirement for prolonged treatment.

Haemolysis has not been previously reported with nitrobenzene but is consistent with known mechanisms.\textsuperscript{5,15-16} In our patient, this may have been more clinically noticeable because of the large ingestion and presumed prolonged exposure. The clinical correlates of intravascular haemolysis characterised by a drop in haemoglobin and increased bite cells are well-accepted. Bite cell haemolytic anaemia is a variant of drug-related haemolysis usually associated with methaemoglobinaemia in red blood cells secondary to oxidant injury.\textsuperscript{17}

In one rabbit study, oral administration of 250 mg [\textsuperscript{14}C] nitrobenzene/kg by stomach tube showed incomplete absorption (66% of the total dose) of nitrobenzene from the intestinal tract. Subsequent radioactivity analysis of body tissues 1.5 days after revealed that 44.5% of the administered dose was distributed in kidney fat (15.4%), intestinal fat (11.6%) and skeletal muscle (12%). Moreover, it took 8 days for radioactivity to come down to <7.5%.\textsuperscript{13} This suggests that systemic redistribution of
nitrobenzene from tissue stores is likely. Initial prehepatic intestinal nitroreduction of nitrobenzene may be the most important factor in the generation of early methaemoglobinaemia as it is 150 times faster than the hepatic microsomal nitroreductase. The slow hepatic microsomal nitroreductase rates suggest that enzyme saturation is possible, which may contribute to prolonged methaemoglobinaemia.

Although glucose-6-phosphate dehydrogenase was not assessed in our patient, the dramatic response of MetHb to MB treatment effectively excludes severe glucose-6-phosphate dehydrogenase deficiency. The total dose of MB our patient received is low and is unlikely to be the cause of haemolysis.

The clinical syndrome associated with MetHb is well-described and is a result of increased tissue hypoxia because of reduced oxygen carrying capacity of MetHb. In cases where there is poor clinical improvement following initial dosing, repeated dosing has been proposed. Although, as seen in our patient, the short half-life of 4.5 hours of MB is ineffective in conditions were there is prolonged oxidative stress due to continuing exposure to nitrobenzene or its metabolites. Moreover, repeated high doses may potentially lead to MB-induced methaemoglobinaemia. Low dose infusions after an initial bolus have been used in such situations.

**LEARNING POINTS**

- Massive nitrobenzene ingestion may lead to recurrent methaemoglobinaemia.
- Dramatic response of methaemoglobin to methylene blue treatment may effectively exclude severe glucose-6-phosphate dehydrogenase deficiency.
- Look for haemolysis in these patients.
- Repeated doses of methylene blue may be required.

**Footnotes**

**Competing interests:** none.

**Patient consent:** Patient/guardian consent was obtained for publication.

**REFERENCES**


Methaemoglobin (MB) concentration following nitrobenzene poisoning. Hb, haemoglobin.
Severe peripheral cyanosis (the lower hand is the patient) following nitrobenzene poisoning.