Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

A fatal case of severe methaemoglobinemia due to nitrobenzene poisoning

Alok Gupta, Nirdesh Jain, Avinash Agrawal, Arjun Khanna, Manish Gutch

Department of Internal Medicine, CSM Medical University, Lucknow, Uttar Pradesh, India

Correspondence to Dr Avinash Agrawal, icuexpert@gmail.com

Summary

An acute poisoning with nitrobenzene presenting as methaemoglobinemia is an uncommon medical emergency. A young girl with nitrobenzene induced methaemoglobinaemia died despite use of mechanical ventilator, administration of oral methylene blue and parenteral ascorbic acid. Here author highlights the rare occurrence of such cases, methaemoglobin induced severe oxidative stress, unexplained splenomegaly and leucocytosis and the ineffectivity of oral methylene blue and other supportive measures in evading death due to nitrobenzene poisoning.

BACKGROUND

Nitrobenzene, an aromatic nitro-compound, occurs as a pale yellow moderately water-soluble oily liquid with an odour resembling that of bitter almonds. It is slightly soluble in water, readily soluble in organic solvents such as alcohol, ether and benzene and highly soluble in lipids. It is used in the manufacture of aniline, benzidine, quinoline, azobenzene, rubber chemicals, drugs and dyes, as a solvent in shoe and metal polishes and in screen-printing. Its toxic effects are due to its ability to induce methaemoglobinemia.¹ An acute poisoning with nitrobenzene presenting with methaemoglobinemia is an uncommon medical emergency. We describe here a fatal case of acute nitrobenzene poisoning in a suicidal attempt by a young girl.

CASE PRESENTATION

A 17-year-girl was admitted with alleged history of consumption of unknown quantity of nitrobenzene 6 h prior to admission. She had four episodes of vomiting and breathlessness and became unconscious 1 h prior to admission. On admission, she was unconscious with a Glasgow Coma Scale of 3, gasping respiration and cyanosis of fingers and tongue, pulse rate 130/min, blood pressure 110/70 mm of mercury and semidilated and sluggish reacting pupils. She was immediately intubated and put on mechanical ventilator.

INVESTIGATIONS

Arterial blood gas (ABG) analysis on admission showed pH 7.26, PaO₂ 29.9 mm of mercury, PaCO₂ 41.8 mm of mercury, HCO₃⁻ 18.3 meq/l, SO₂ 44.6%. Her haemoglobin (Hb) was 8.8 gm%, total leucocyte count (TLC) 8000/mm³, normal differential count, platelet count 2 40 000/mm³. Renal function tests, liver function tests, serum electrolytes, urine, ECG and chest x-ray were all normal. Methaemoglobin level was 63.3% (normal: 1%), free sulphhydryl group (SH) levels were 0.188 µmol/ml blood (normal: 12.08–18.59), glutathione (GSH) level was 0.257 µmol/g Hb (normal: 3.5–11.5), superoxide dismutase level was 19.65 nmol

epinephrine oxidase/min/g Hb (normal: 23.81–92.51), lipid peroxidation 10.31nmol malondialdehyde/h/ml plasma (normal: 0.89–1.31). She was administered 100 mg (2 mg/kg) of oral methylene blue and ascorbic acid 500 mg intravenously every 12 h. Repeat ABG after 1 h showed pH 7.36, PaO₂ 56.6 mm of mercury, PaCO₂ 34.4 mm of mercury, HCO₃⁻ 19.63 meq/l, SO₂ 83.2% and methaemoglobin 36.6%. Repeat ABG after 24 h showed pH 7.423, PaO₂ 75 mm of mercury, PaCO₂ 34.2 mm of mercury, HCO₃⁻ 19.4 meq/l, SO₂ 94% and methaemoglobin 47.7%. During next 2 days she did not regain consciousness, cyanosis increased, she developed a 4 cm palpable spleen and her oxygen saturation decreased to 66%.

Methaemoglobin was 76.5%, Hb 7.2 gm%, TLC 56 600/mm³ with neutrophil predominance, platelet count 76000/mm³, serum urea 122 mg%, serum creatinine 3.4 mg%, serum bilirubin 2.6 mg% and a three times rise in transaminases. On autopsy, petechial haemorrhages were found in both cerebral hemispheres, liver and spleen were congested and histopathological examination showed evidence of renal tubular necrosis and hepatic centrilobular necrosis.

TREATMENT

She was administered 100 mg (2 mg/kg) of oral methylene blue and ascorbic acid 500 mg intravenously every 12 h. We used oral methylene blue as that was readily available and the patient had signs of severe intoxication, we thought that it was prudent not to wait for intravenous methylene blue, which is not readily available in our setting.

OUTCOME AND FOLLOW-UP

She expired on fourth day of admission.

DISCUSSION

Nitrobenzene ingestion oxidises iron in haemoglobin to form methaemoglobin. The level of methaemoglobin in blood is about 1% and level above this is called methaemoglobinemia.

The low level of MeHb is maintained by two important mechanisms.² One is the hexose monophosphate shunt pathway within the erythrocyte by which oxidising 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 (NADH) methaemoglobin reductase) and diaphorase II (nicotinamide adenine dinucleotide phosphate (NADPH) methaemoglobin reductase). These two enzyme systems require NADH and NADPH, respectively to reduce MeHb to its original ferrous state. Diaphorase II quantitatively contributes only a small percentage of the reducing capacity of RBC. Methaemoglobinemia occurs when excessive oxidative stress produce methaemoglobin at a rate that overwhelms the capacity to reduce it through enzyme systems. The estimated lethal dose ranges from 2 to 6 g in adults; and doses less than 0.8 mg/kg/day does not normally cause methaemoglobinaemia.³ In normal individuals methaemoglobin level must be greater than 10% to be clinically recognised and only mild symptoms, headache, fatigue and nausea occur at level of 20%–30%. Dyspnoea on exertion, lethargy and tachycardia occur at 30% to 45% levels, and at 50% to 70%, arrhythmias, coma, seizures, respiratory distress and lactate acidosis. Levels greater than 70% cause cardiovascular collapse and have a high degree of mortality if left untreated.³ Methylene blue is the antidote of choice for acquired (toxic) methaemoglobinemia.⁴ It acts as an exogenous co-factor which greatly accelerates the NADPH dependent methaemoglobin reductase system.⁴ The initial dose is 1 to 2 mg/kg or 0.1 to 0.2 ml/kg of the 3% solution given intravenously over 5 min. In higher doses, methylene blue itself is an oxidising agent and as little as 5 mg/kg has caused asymptomatic methaemoglobinemia.⁵ Cumulative doses greater than 7 mg/kg have an increased risk of methaemoglobin induction.

We have observed that nitrobenzene ingestion resulted in severe oxidative stress as suggested by increased levels of methaemoglobin, decrease in the levels of free SH, GSH, superoxide dismutase and increase in lipid peroxidation. Administration of methylene blue resulted in slight decrease in the level of methaemoglobin early, but the levels were again high on second day. Delayed release of nitrobenzene from stores in the adipose tissue and

gastrointestinal tract is commonly seen after severe poisoning² and may be responsible for this deterioration. Another finding that remains unexplained is that why the patient developed severe leukocytosis and splenomegaly. The present case represents an uncommon poisoning with nitrobenzene, which could not be managed successfully with oral methylene blue and ascorbic acid along with intensive haemodynamic and cardiopulmonary support.

Learning points

- ▶ Nitrobenzene ingestion results into severe oxidative stress as suggested by increased levels of methaemoglobin, decrease in the levels of free SH, GSH, superoxide dismutase and increase in lipid peroxidation.
- ▶ Delayed release of nitrobenzene from stores in the adipose tissue and gastrointestinal tract is commonly seen after severe poisoning and may be responsible for delayed catastrophe.
- ▶ Unexplained severe leukocytosis and splenomegaly can be seen in case of nitrobenzene poisoning.
- ▶ The present case represents an uncommon poisoning with nitrobenzene, which could not be managed successfully with oral methylene blue and ascorbic acid along with intensive haemodynamic and cardiopulmonary support.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Wright RO**, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology and clinical management. *Ann Emerg Med* 1999;**34**:646–56.
2. **Patel A**, Dewan KJ, Upadhyay SA, et al. Chemically induced methemoglobinemia from acute nitrobenzene poisoning. *The Internet Journal of Laboratory Medicine* 2009;**3**:2.
3. **Chongtham DS**, Phurailatpam J, Singh MM, et al. Methaemoglobinemia in nitrobenzene poisoning. *J Postgrad Med* 1997;**43**:73–4.
4. **Curry S**. Methemoglobinemia. *Ann Emerg Med* 1982;**11**:214–21.
5. **Whitwan JG**, Taylor AR, White JM. Potential hazard of methylene blue. *Anaesthesia* 1979;**34**:181–2.

This pdf has been created automatically from the final edited text and images.

Copyright 2011 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Gupta A, Jain N, Agrawal A, Khanna A, Gutch M. A fatal case of severe methaemoglobinemia due to nitrobenzene poisoning.

BMJ Case Reports 2011;10:1136/bcr.07.2011.4431, date of publication

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow