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

Acute cardiogenic pulmonary oedema with multiorgan dysfunction – still to learn more about nitrobenzene poisoning

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Summary

Nitrobenzene is a nitrite compound often used in polishes or solvents. Its toxic effects are due to its ability to induce methaemoglobinaemia. The clinical presentation of this poisoning varies according to the concentration of methaemoglobin level in blood. The importance of early identification of the compound on the basis of clinical suspicion corroborative with methaemoglobin level with timely intervention is required to prevent fatal outcome. It is also important to take care of the secondary cycling of nitrobenzene from body stores to prevent secondary recurrence of symptoms in patients after heavy exposure. Here author reports a rare case of accidental poisoning with nitrobenzene presented with respiratory distress and cyanosis. On investigation, he was diagnosed to have cardiogenic pulmonary oedema and multiorgan dysfunction. The urgent institution of methylene blue as specific antidote along with haemodynamic and ventilatory support was proved crucial for life saving of the patient.

BACKGROUND

Nitrobenzene poisoning can have varied clinical manifestation, the spectrum depends on the concentration of methaemoglobin level in blood and it range from only mild symptoms; headache, fatigue, nausea to life-threatening events such as arrhythmias, coma, seizures, respiratory distress, lactate acidosis and cardiovascular collapse. Here author highlights a case of acute cardiogenic pulmonary oedema with multiorgan dysfunction due to nitrobenzene poisoning which could be fatal if not timely identified and treated with methylene blue and cardiopulmonary support.

CASE PRESENTATION

A 32-year-old male working in a printing press brought to medical emergency in state of respiratory distress with cold clammy skin with history of accidental consumption of around 100 ml of a dye containing nitrobenzene about 7 h back. On examination, he was pale cyanosed, with poor respiratory efforts, not responding even to painful stimuli with peripheral pulses and blood pressure being non-recordable with engorged neck veins. On systemic examination, the precordium was quiet, with a weak apical pulse. S_1 was soft, and an S_3 gallop was audible and central venous pressure was 26 mm Hg. There were bilateral coarse crepitations with rales audible in whole of the chest with rest of the other systems within normal limit. The patient did not have any significant past and family history of cardiovascular disease. On this background of acute cardiopulmonary compromise, arterial blood analysis was done which showed type 1 respiratory failure with severe metabolic acidosis and high lactate level 11.7 (<1.0). With this clinical scenario, the patient diagnosed as a case of acute cardiogenic pulmonary oedema and due to

poor respiratory efforts patient put on mechanical ventilation (volume control ventilatory mode) and vasopressor support.

INVESTIGATIONS

Arterial blood gas (ABG) analysis showed pH 7.00, pO_2 37 mm Hg, pCO_2 30 mm Hg, HCO_3^- 7.4 mmol/l, lactate 11 mmol/l suggestive of type 1 respiratory failure. Chest x-ray (figure 1) showed bilateral fluffy deposits with cardiomegaly suggesting cardiogenic pulmonary oedema. An ECG (figure 2) was also done at that time showed inferior wall myocardial ischaemia. By the mean time, other investigations were also available which showed Troponin T-1.96 (<0.01), N-terminal pro-B-type natriuretic peptide (NT pro BNP) 3225 (<125.0), haemoglobin-11.8 gm%, total leucocyte count-12600/mm³, differential leucocyte count-P72 L18, platelet count-1.39 lakhs, random blood sugar-83 mg/dl, serum bilirubin-1.4 mg%, serum glutamic oxaloacetic transaminase-642, serum glutamic pyruvic transaminase-487, serum alkaline phosphatase-667 and serum methaemoglobin level were 65% ($<1\%$). Fasting lipid profile was within normal limit. 2D echocardiography was done on the day 4 which revealed normal cardiac structures (figure 3a,b). The patient was regularly followed by intensive blood pressure monitoring along with serial ABG to monitor the response to therapy which is shown in table 1. During the hospital stay, the patient made uneventful recovery and was discharged on 7th day.

TREATMENT

The patient was started on vasopressors in form of intravenous dopamine (10 µg/kg body weight) and dobutamine (5 µg/kg body weight) and methylene blue at a dose of 2 mg/kg body weight for the first day and 1 mg/kg for next

Figure 1 On the day of admission, chest x-ray posteroanterior view shows cardiomegaly with bilateral fluffy infiltrate involving whole of the lung field.

Figure 2 ECG at the time of presentation shows ST segment elevation in lead II, III and a VF with corresponding ST depression in lead V1, V2 and V3 suggestive of inferior wall myocardial ischaemia.

2 days, oral vitamin C supplementation at dose of 500 mg twice daily was also given along with methylene blue for 3 days. He was also required to be put on mechanical ventilation (volume control ventilatory mode) for 2 days.

OUTCOME AND FOLLOW-UP

The patient was vigorously managed in the medical intensive care unit with improvement of cardiopulmonary parameters within 3 days so as ventilatory support was

Figure 3 2 D echocardiography, apical 4 chamber view shows normal mitral inflow (a) and normal tricuspid inflow (b) on 4th day of admission.

withdrawn within 2 days and vasopressor support within 3 days and the patient was discharged on 7th day.

DISCUSSION

Nitrobenzene is an oxidising nitrite compound. Acute ingestion of nitrobenzene leads to rapid development of methaemoglobinaemia, a condition in which the iron within the haemoglobin is oxidised from the ferrous (Fe^{2+})

state to the ferric (Fe^{3+}) state, resulting in the inability to transport oxygen and causes a brownish discolouration of the blood.¹ Once formed, methaemoglobin can be reduced enzymatically either via an adenine dinucleotide (NADH)-dependent reaction, catalysed by cytochrome b5 reductase, or an alternative pathway using the nicotine adenine dinucleotide phosphate (NADPH)-dependent methaemoglobin reductase system.² Methaemoglobin is normally present as

Table 1 Displaying patient's arterial blood gas, ventilatory settings, blood pressure and vasopressors requirement during course of hospital stay

Parameters	pH (7.35–7.45)	pCO ₂ (35–45 mm Hg)	pO ₂ (80–100 mm Hg)	HCO ₃ (20–24 mmol/l)	Lactate (<1 mmol/l)	SO ₂	Ventilator	BP (mm Hg)	Dopamine (µg/kg B.W)	Dobutamine (µg/kg B.W)
Day 1										
At 1 h	7.00	30	37	7.4	11	55	VCV	N.R.	10	5
At 2 h	7.25	26	125	11.4	11.7	98	VCV	N.R.	10	5
At 12 h	7.23	31	48	13	7.6	74	VCV	70s BP	10	5
At 15 h	7.2	32	43	14.4	6.9	70	VCV	80s BP	5	5
Day 2	7.42	30	359	19.5	1.9	100	VCV	90/60	4	4
Day 3	7.45	43	36	29.9	2.1	72	no	120/70	-	2
Day 4	7.51	33	97	26.3	1.4	98	no	122/88	-	-
Day 5	7.45	37	63	25.7	2.2	93	no	130/80	-	-
Day 6	7.38	37	66	24.7	1.2	96	no	126/74	-	-
Day 7	Discharged with advise to follow-up OPD regularly									

BP, blood pressure; B.W, body weight; N.R, not recordable; OPD, outpatient department; VCV, volume controlled ventilation.

less than 1% of the total haemoglobin under physiologic conditions.³ Levels above it are defined as methaemoglobinemia. 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 methaemoglobinemia.⁴ 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%.⁵ Dyspnoea on exertion, lethargy and tachycardia at 30 to 45% levels, and at 50 to 70%, arrhythmias, coma, seizures, respiratory distress and lactate acidosis are seen. Levels greater than 70% cause cardiovascular collapse and have a high degree of mortality if left untreated.⁶ With significant nitrobenzene poisoning with methaemoglobinemia, ABG analysis reveals lactate metabolic acidosis, tissue ischemia and hypoxia. PaO₂ remains normal, measured (not calculated) oxygen saturation will be low.¹ Liver stomach, blood and brain may act as stores and release it gradually.⁷

Clues for diagnosis include a history of chemical ingestion, the characteristic smell of bitter almonds, persisting cyanosis on oxygen therapy, low arterial oxygen saturation, with normal ABG (calculated) oxygen saturation. Dark brown blood that fails to turn bright red on shaking, which suggests methaemoglobinemia and this is supported by the chocolate red colour of dried blood. Presence of nitrobenzene compounds may be confirmed spectrophotometrically and methaemoglobin levels in the blood. The severity of symptoms may not correlate with the degree of methaemoglobinemia.⁸ Cyanosis is clinically detected when the absolute concentration of methaemoglobin exceeds 1.5 g/dl, equivalent to 8–12% methaemoglobin (at normal haemoglobin concentrations). Pulse oximetry is inaccurate in monitoring oxygen saturation in the presence of methaemoglobinemia.⁹

Recommended treatment is based on the principles of decontamination and symptomatic and supportive management. Methylene blue is the antidote of choice for the acquired (toxic) methaemoglobinemia. It is an exogenous cofactor, which greatly accelerates the NADPH-dependant methaemoglobin reductase system and is indicated if the methaemoglobin levels, which are more than 30%.¹⁰ It is administered intravenously at 1–2 mg/kg (up to 50 mg dose in adults,) as a 1% solution over 5 min; with a repeat in 1 h, if necessary. Response occurs within 1 h and reduces the elimination half-life of severe methaemoglobinemia to 45–90 min. Methaemoglobin levels should be checked 1 h

after infusion and a repeat dose may be warranted if levels remain high and the patient is still symptomatic. Methylene blue is an oxidant at levels of more than 7 mg/kg, and therefore, may cause methaemoglobinemia in susceptible patients. It is contraindicated in patients with G6PD deficiency, because it can lead to severe haemolysis. Ascorbic acid is an antioxidant that may also be administered in patients with methaemoglobin levels of more than 30%.¹¹ In recent studies, N-acetylcysteine has been shown to reduce methaemoglobin, but it is not yet an approved treatment for methaemoglobinemia. Exchange transfusion is indicated in severe cases.¹⁰ Hyperbaric oxygen is reserved only for those patients who have a methaemoglobin level >50% or those who do not respond to standard treatment.³

In the present scenario, the patient presented in shock with cardiogenic pulmonary oedema which is evidenced by raised Troponin T,¹² a marker of cardiomyocyte injury, raised NT pro BNP,¹³ an early marker of cardiac dysfunction, abnormal ECG showing inferior wall ischaemia and echocardiography did not reveal any sign of regional wall motion abnormality, suggesting that some form of cardiac injury is induced by nitrobenzene due to some unknown mechanism. Various hypotheses for such type of tissue injury have been suggested such as free radical injury or methaemoglobinemia induced hypoxic injury which are not yet proven.¹⁴

In nitrobenzene poisoning, effects on liver are low total plasma proteins with increased albumin/globulin ratio, increased indirect bilirubin levels with variable elevations of liver enzymes, decrease in cholesterol esters and slight but significant bromosulphophthalein retention. The liver was enlarged and tender and excessive aminoaciduria indicates liver damage. Histological finding shows liver atrophy with parenchymatous degenerative and necrotic foci, may be a sequela of severe poisoning.¹⁵

Timely identification of the compound with active intervention and specific antidote in form of methylene blue has lead to rapid reversal of toxic effects of the compound. Due to financial constrain, angiography could not be done. Taking care of nutrition, adequate urine output, and hepatoprotection prevented further deterioration of kidney and liver functions, which have been cited as late effects.¹⁶ Forced diuresis led to a rapid fall in methaemoglobin levels and improved discolouration.⁹ Ascorbic acid supplements are useful for follow-up management of methaemoglobinemia.⁷

The present index case represents an uncommon poisoning with nitrobenzene, which was managed successfully with intravenous methylene blue and ascorbic acid with intensive haemodynamic and cardiopulmonary support.

Learning points

- ▶ Nitrobenzene poisoning should be considered as differential diagnosis in case of cyanosis of obscure aetiology.
- ▶ Nitrobenzene poisoning can cause cardiac tissue injury presenting as cardiogenic pulmonary oedema which can be reversed by timely identification of the compound by serum methaemoglobinaemia and early treatment with methylene blue leading to rapid reversal of symptomatology.
- ▶ Methylene blue is specific antidote, should be started promptly to combat the toxic effects of nitrobenzene poisoning. Life saving supports are paramount and should be considered along with methylene blue.
- ▶ We should be watchful to prevent secondary methaemoglobinaemia which might occur due to cycling of nitrobenzene in the body stores.

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REFERENCES

1. **Schimmelman MA**, Soler JM, Muller HA. Methemoglobinemia: nitrobenzene ingestion. *JACEP* 1978;**7**:406–8.
2. **Dutta R**, Dube SK, Mishra LD, *et al.* Acute methemoglobinemia. *Internet J Emerg Intensive Care Med* 2008;**11**:1092–4051.
3. **Mansouri A**. Methemoglobinemia. *Am J Med Sci* 1985;**289**:200–9.
4. **Harris JC**, Rumack BH, Peterson RG, *et al.* Methemoglobinemia resulting from absorption of nitrates. *JAMA* 1979;**242**:2869–71.
5. **Walley T**, Flanagan M. Nitrite-induced methaemoglobinaemia. *Postgrad Med J* 1987;**63**:643–4.
6. **Eisen Kraft JB**. Pulse oximeter desaturation due to methaemoglobinemia. *Anaesthesiology* 1988;**68**:279–82.
7. **Gupta G**, Poddar B, Salaria M, *et al.* Acute nitrobenzene poisoning. *Indian Pediatr* 2000;**37**:1147–8.
8. **Wright RO**, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. *Ann Emerg Med* 1999;**34**:646–56.
9. **Sinex JE**. Pulse oximetry: principles and limitations. *Am J Emerg Med* 1999;**17**:59–67.
10. **Chongtham DS**, Phurailatpam J, Singh MM, *et al.* Methaemoglobinemia in nitrobenzene poisoning. *J Postgrad Med* 1997;**43**:73–4.
11. **Curry S**. Methemoglobinemia. *Ann Emerg Med* 1982;**11**:214–21.
12. **Katus HA**, Remppis A, Neumann FJ, *et al.* Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation* 1991;**83**:902–12.
13. **Maeda K**, Tsutomoto T, Wada A, *et al.* Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998;**135**(5 Pt 1):825–32.
14. **De Bruin A**. *Biochemical Toxicology of Environmental Agents*. New York: Elsevier/North Holland Inc. 1976.
15. **Parkes WE**, Neill DW. Acute nitrobenzene poisoning with transient amino-aciduria. *Br Med J* 1953;**1**:653–5.
16. **Kaushik P**, Zuckerman SJ, Campo NJ, *et al.* Celecoxib-induced methemoglobinemia. *Ann Pharmacother* 2004;**38**:1635–8.

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