



## Management of nitrobenzene poisoning with oral methylene blue and vitamin C in a resource limited setting: A case report

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### ABSTRACT

Nitrobenzene can cause life threatening methaemoglobinemia. Its management includes the use of intravenous methylene blue to reduce the iron moiety from its ferric to ferrous state. Due to unavailability of intravenous preparation, enteral methylene blue was used in our case. This case report is to highlight that even oral preparations can be successfully used in a resource limited setting where often intravenous preparations are unavailable.

### 1. Introduction

Nitrobenzene ("nitrobenzol" or "oil/essence of mirbane") is a pale yellow aromatic nitro compound frequently used in synthetic rubber, dye and paint industries [1]. It is a potent oxidizer of the iron moiety of haemoglobin causing methaemoglobinemia leading to its inability to transport oxygen [2]. Clinical features of nitrobenzene poisoning include gastric irritation, nausea, vomiting, cyanosis, drowsiness, seizures, coma and finally respiratory failure culminating in death [3]. Intravenous methylene blue and vitamin C are commonly used for treatment of significant poisoning [4]. We report a case of severe nitrobenzene poisoning who was managed and discharged home with oral preparations of methylene blue and vitamin C.

### 2. Case report

A 45 years female with chronic alcoholism, had presented to a primary center with low Glasgow coma scale (GCS) of 7/15 (E2 = eye opening to pain, V2= incomprehensible sounds, M3 = abnormal flexion). She had a history of ingestion of about 50 ml of 20 % nitrobenzene solution while under the influence of alcohol with an alleged suicidal intent. She was intubated at another center and was referred to us for further management.

In the emergency department(ED) of our center, she had a GCS of 2/

10 T (E1= no eye reponse, VT = endotracheal intubation, M1= no motor response) and was under manual bag and endotracheal tube ventilation. Her arterial oxygen saturation showed 80 % with clinically evident central and peripheral cyanosis. Her pulse rate was 130 beats per minute and blood pressure was 90/70 mmHg. An arterial blood gas analysis showed a pH of 6.98, PCO<sub>2</sub> of 34 mm of Hg, bicarbonate of 8mEq/L, lactate of 8 mmol/L and PO<sub>2</sub> of 170 mm of Hg.

She was transferred to the intensive care unit (ICU) where on the background of severe metabolic acidosis, sodium bicarbonate infusion was started. Noradrenaline infusion was started for hypotension which was gradually tapered off in a few hours. Haemodialysis was initiated for severe metabolic acidosis via a dialysis catheter inserted in the right femoral vein.

Meanwhile, a preparation of methylene blue was initiated enterally through the orogastric tube at a dose of 2 mg/kg (total 100 mg) and repeated after 12 h. Oral vitamin C 1.5 gm immediately and three times a day thereafter was started. Oral preparations for both drugs were used due to unavailability of intravenous preparations. Intravenous thiamine 100 mg immediate and three times daily was started in view of the patient's history of chronic alcoholism.

The acidosis resolved after three sessions of dialysis. Mechanical ventilation was gradually weaned to a fraction of inspired oxygen (FiO<sub>2</sub>) of 40 % with a positive end expiratory pressure (PEEP) of 5 cm of water (H<sub>2</sub>O) maintaining a targeted SpO<sub>2</sub> of more than 90 %. She was

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extubated after 30 h of mechanical ventilation. Urine output was maintained at 1–2 ml/kg/hr.

The patient was transferred to the ward on the fourth day and discharged home on the sixth on oral thiamine and vitamin C.

### 3. Discussion

Nitrobenzene is easily absorbed from the respiratory tract, the gastrointestinal tract or the skin following intentional or accidental exposure. It is highly lipophilic because of which the highest concentrations get accumulated in the liver, brain, blood and stomach [5]. In the blood, it leads to the excessive oxidation of the iron moiety of the haemoglobin molecule forming methaemoglobin. This molecule has an oxidized iron moiety ( $\text{Fe}^{3+}$ ) instead of the usual reduced form ( $\text{Fe}^{2+}$ ). This methaemoglobin molecule is incapable of oxygen transport. During physiological states, less than 1 % of the total hemoglobin is oxidized to methaemoglobin. This low level is maintained mainly because of two reductive pathways present in the red blood cells namely the hexose monophosphate (HMP) pathway and the diaphorase pathways. With increase in oxidative stress as when occurs during nitrobenzene poisoning, these pathways are overwhelmed leading to increased proportions of methaemoglobin [2]. As a result, the  $\text{SpO}_2$  falls despite a high  $\text{PaO}_2$  leading to the classical description of chocolate brown blood failing to redden even on exposure to ambient air [6]. The clinical symptoms are graded according to the methaemoglobin levels. Mild symptoms of headache, fatigue and nausea occur at 20–30 %; dyspnea, lethargy and tachycardia occur at 30–45 %; arrhythmias, coma, seizures, respiratory distress and lactate acidosis occur at 50–70 %; cardiovascular collapse and death occur at levels greater than 70 %. The lethal dose reported ranges from 1 to 10 gm [2].

The resultant effect is hypoxic tissue injury despite a normal  $\text{PaO}_2$ . This causes severe lactic acidosis from the metabolic switch to anaerobic respiration, hypoxic liver injury as evidenced by increased liver enzymes, hypoxic encephalopathic changes which may be irreversible and acute kidney injury [1,7].

Although methaemoglobin level measurement was not possible, the classic findings of a reduced  $\text{SpO}_2$  with cyanosis but normal  $\text{PO}_2$  that did not improve with administration of supplemental oxygen were adequate evidences of clinically significant methaemoglobinemia in the background of history of nitrobenzene ingestion.

The management has two aspects: first, to restore normal physiological conditions with supportive management and second, to attempt to decrease the methaemoglobin level. The first includes administration of sodium bicarbonate and intermittent haemodialysis to attenuate metabolic acidosis, endotracheal intubation and IPPV for oxygenation and use of vasopressors for tissue perfusion [3,8]. The second entails the usage of methylene blue and rarely exchange transfusion [9]. Although ample evidence of intravenous methylene blue is present in literature supporting its use, we had to resort to enteral administration due to its unavailability. Very limited experience is present for the use of oral methylene blue in nitrobenzene poisoning [10]. The bioavailability for oral methylene blue has been found to be around 72 % and based on its usage for other therapies, a dose of 2 mg/kg (100 mg) which has been found to be both safe and effective was chosen for our patient [11]. Vitamin C further decreases the oxidative stress acting as an oxygen

scavenger which too was administered orally due to its unavailability in intravenous form. Her improvement after oral methylene blue administration is suggestive that this route of administration is a viable option for treatment when the intravenous preparation is not available.

### 4. Conclusion

Nitrobenzene poisoning in a resource limited setting can cause therapeutic inadequacies due to unavailability of intravenous methylene blue and vitamin C preparations. However even oral preparations can be effective in the successful management as evident in our case.

#### Ethical approval

Not applicable.

#### Consent for publication

Written informed consent was taken from the patient herself for publication of this case report.

#### Declaration of Competing Interest

The authors report no declarations of interest.

#### Acknowledgment

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