

## Reminder of important clinical lesson

Pop goes the O<sub>2</sub>: a case of popper-induced methaemoglobinamiaAileen McCabe,<sup>1</sup> Brendan McCann,<sup>1</sup> Paul Kelly<sup>2</sup><sup>1</sup>Emergency Department, Waterford Regional Hospital, Waterford, Ireland<sup>2</sup>Emergency Department, Wexford General Hospital, Wexford, IrelandCorrespondence to Dr Aileen McCabe, [aileenmccabe@rcsi.ie](mailto:aileenmccabe@rcsi.ie)**Summary**

A 39-year-old man presented to the emergency department after falling downstairs after he consumed a large quantity of alcohol. On examination, he had altered mental state (GCS 14), central cyanosis and low oxygen saturation of 86%, despite 100% oxygen being administered. His arterial blood gas confirmed diagnosis of methaemoglobinaemia with a methaemoglobin percentage of 14.08. He was treated successfully with methylthioninium chloride. The patient later admitted to use of recreational poppers (amyl nitrates) the previous evening. The emergency physician is challenged by the presentation of a patient with altered mental state and unexplained low oxygen saturation with concurrent alcohol intoxication but must have a high index of suspicion for methaemoglobinaemia particularly with a history of recreational drug ingestion.

**BACKGROUND**

The emergency physician is faced with many challenges when assessing a patient with altered mental state particularly when confounded with suspected alcohol intoxication.

Diagnosis of methaemoglobinaemia is very difficult unless there is a high index of suspicion particularly if the patient presents with a history of drug ingestion and has low oxygen saturation despite administration of 100% oxygen.

**CASE PRESENTATION**

A 39-year-old man presented to the emergency department, by ambulance, after falling down a flight of stairs after consuming a large quantity of alcohol. He had hit his head and was complaining of headache. He denied any loss of consciousness. He had a medical history of alcohol dependency and gastritis. He initially denied any illegal drug misuse.

On examination, the patient appeared to be intoxicated and combative with medical staff. His heart rate was 101 beats/min, temperature 36.7° centigrade, blood pressure 135/87 mm Hg. He had blue discolouration to his lips and his oxygen saturation was 86%, despite being administered 100% oxygen through a non-rebreather mask. His Glasgow coma score was 14 (E4 M6 V4). On respiratory examination, he had good air-entry in all pulmonary zones. He had a small laceration on his forehead but no clinical signs of base of skull fracture (ie, no battle's sign, raccoon eyes or haemotympanum).

**INVESTIGATIONS**

Initial arterial blood gas (ABG) pH 7.41, pO<sub>2</sub> 17.33 kilopascals (kPa), pCO<sub>2</sub> 5.39, MetHb 14%, base excess 1.0, bicarbonate 25.5 mmol/l. CT imaging of his head reported no acute brain injury.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnosis considered for the altered mental state included:

- ▶ Traumatic brain injury
- ▶ Alcohol/ illicit drug intoxication
- ▶ Anoxic brain injury secondary to ventilation/perfusion mismatch, for example, secondary to pneumonia, pulmonary embolism.

Differential diagnosis, considered after the results of the ABG, reported the methaemoglobinaemia which was deemed likely to be acquired included

- ▶ Volatile nitrites (poppers)
- ▶ Dapsone
- ▶ Sulphonamides.

**TREATMENT**

He was administered 100% oxygen through a non-rebreather mask and he was administered 10 ml of 1% methylene blue.

**OUTCOME AND FOLLOW-UP**

His follow-up ABG post-treatment was pH 7.36, pO<sub>2</sub> 10 kPa, pCO<sub>2</sub> 6.10 kPa, MetHb 0.8%. When the patient was sober, his history was taken again. This time, he admitted to use of illegal poppers the night before and use of cocaine in the past. He was observed for 6 hours post-treatment and discharged with advice to avoid poppers or any products containing alkyl nitrites.

**DISCUSSION**

This report demonstrates a case of methaemoglobinaemia secondary to the recreational use of 'poppers' presenting as altered mental state and unexplained low oxygen saturation to the emergency department.

Methaemoglobin is formed by oxidation of the haem molecule, from its reduced Fe<sup>2+</sup> (ferrous) state to an oxidised Fe<sup>3+</sup> (ferric) state via a NADPH-dependent pathway

which is incapable of binding oxygen for transport. The presence of methaemoglobin in the erythrocyte structurally alters haemoglobin further affecting unaffected haem-molecules availability for oxygen transportation by increasing affinity for oxygen which impairs oxygen off-loading to the tissues.<sup>1</sup> Normal blood levels are 0–2%.

Methaemoglobinaemia can rarely be caused by congenital defects in the haemoglobin molecular structure and the erythrocyte metabolism.<sup>2</sup>

In an acute presentation, methaemoglobinaemia is generally acquired, secondary to the oxidising effects of exogenous substances including local anaesthetic agents (lignocaine, prilocaine), dapsone, sulphonamides and phenacetin.<sup>3–5</sup> The primary recreational agents which cause methaemoglobinaemia are volatile nitrites (poppers) and cocaine which have been adulterated with agents such as local anaesthetics or phenacetin.<sup>6</sup>

Initially, the use of amyl nitrate was pioneered by Thomas Brunton in the nineteenth century for the treatment of angina pectoris.<sup>7</sup>

However, the volatile nitrites (particularly, isopropyl nitrite, isobutyl nitrite, butyl nitrite and amyl nitrite) have been used increasingly for the vasodilator effects, since the seventies, for recreational purposes and known as its street name ‘poppers’.<sup>8–9</sup> In particular, their use is prevalent among men who have sex with men as they act as anal sphincter relaxant and heighten sexual experience.<sup>10</sup>

Diagnosis of methaemoglobinaemia is made by doing ABC analysis which typically reports normal partial pressures of oxygen and carbon dioxide, a normal ‘calculated’ haemoglobin oxygen saturation, an increased methaemoglobin concentration and, in severe cases, a metabolic acidosis.<sup>11</sup>

Conventional two wavelength pulse oximeters are not reliable to indicate the level of methaemoglobin concentration but typically there is a ‘saturation gap between the oxygen saturation on the pulse oximeter and the calculated haemoglobin oxygen saturation on the ABG.’<sup>12</sup> The ABG measures dissolved oxygen concentrations and so is unaffected by dyshaemoglobins.

In the last 10 years, newer pulse oximeters use eight wavelengths of light to measure percentage levels of methaemoglobin accurately and have been used to detect methaemoglobinemia early by anaesthetists.<sup>13–14</sup>

In a comprehensive review, Hunter *et al*<sup>1</sup> found 26 reports of methaemoglobinaemia secondary to inhalation and/or ingestion of volatile nitrites including three reported deaths. The same review found four reports of methaemoglobinaemia related to adulterants added to cocaine. Hunter *et al* categorised typical clinical features according to level of percentage of methaemoglobin. Our patients typified mild-to-moderate methaemoglobinaemia with central cyanosis, central not improving with oxygen administration. In cases with methemoglobinaemia levels greater than 50%, the patient typically has tachypnoea, metabolic acidosis, dysrhythmias, seizures and central nervous system depression/coma.<sup>15</sup> Levels greater than 70% are associated with grave hypoxic symptoms and death.<sup>16</sup>

Treatment begins with securing the airway and maintaining high-flow oxygen to maximise oxygen carriage by the remaining ferrous haem. Definitive treatment is pharmacological with methylene blue which acts as a

substrate for NADPH-MetHb reductase, resulting in the formation of reduced methylthionium chloride which acts as an electron donor to reduce Fe<sup>3+</sup> back to Fe<sup>2+</sup>. Methylene blue is provided as a 1% solution (10 mg/mL). Methylthionium chloride is administered intravenously at a dose of 1–2 mg/kg (0.2 mL/kg of a 1% solution) over 5 min.<sup>17</sup>

Symptomatic improvement usually occurs in the first hour, but a repeat dose can be given in very severe cases. The dose can be repeated hourly as required. Although methylthionium chloride is recommended for patients with levels greater than 30%, it was given to our patient as he was having symptomatic hypoxia.

Methylthionium chloride should be used with caution in individuals with G6PD deficiency, which is more common in individuals of African, Asian and Mediterranean descent owing to low levels of NADPH and it may precipitate haemolysis.<sup>18</sup>

### Learning points

- ▶ It is important to take a good history and maintain a high index of suspicion for relatively uncommon diagnoses in patients with a common presentation.
- ▶ Physicians need to have a high index of suspicion of methaemoglobinaemia if the patient has persistently low oxygen saturation and a history of drug ingestion.
- ▶ Diagnosis is confirmed with an arterial blood gas documenting the methaemoglobin percentage.
- ▶ Newer pulse oximeters using eight wavelengths of light can also be used to detect methaemoglobinaemia early.
- ▶ Treatment is with methylthionium chloride (methylene blue).

**Competing interests** None.

**Patient consent** Obtained.

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