Extreme methaemoglobinaemia secondary to recreational use of amyl nitrite

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INTRODUCTION

Haemoglobin is continuously oxidized from the ferrous (Fe²⁺) to the ferric (Fe³⁺) form and reduced back again. The ferric (Fe³⁺) form, termed methaemoglobin (MetHb), is incapable of transporting oxygen. In the normal physiological state the concentration of methaemoglobin is less than 1%. Figure 1 illustrates the physiological reactions responsible for the reduction of MetHb back to Hb. It is reported that MetHb levels of 10–25% produce cyanosis, 35–40% produce mild symptoms (e.g. dyspnoea), levels of 60% produce lethargy and coma and levels of 70% or more are lethal. A case of extreme, life-threatening methaemoglobinaemia due to the recreational use of amyl (isobutyl) nitrite is presented. No case has been found in the literature where the MetHb level was so high.

Key words: amyl nitrate, methaemoglobinemia, methylene blue

CASE REPORT

A 44-year-old man was brought by ambulance to St Vincent’s Hospital Emergency Department at 23.37 hours. The patient had been found in the steam room of a bathhouse, unconscious, blue and lying in a pool of vomitus. There was an empty bottle of amyl (isobutyl) nitrite next to him, and workers at the establishment stated that he had 'consumed' large amounts of amyl nitrite.

On arrival of the paramedics, the patient was hypoventilating, hypotensive, unresponsive to pain and had poor skin colour. There was no response to 2 mg of naloxone, administered intravenously. The patient was intubated endotracheally by the paramedics, given 100% oxygen, ventilated manually and transported to hospital.

On arrival at the Emergency Department his skin was noted to be a deep charcoal grey colour, despite the fact that he was receiving 100% oxygen and having good air entry into both lungfields on inspiration. His heart rate was 46/min, blood pressure 98/62 mmHg, respiratory rate 10/min, temperature 36.7°C, and his SpO₂ was 99% on 100% oxygen.

His chest X-ray showed no abnormality and his electrocardiogram revealed normal sinus rhythm with a rate of 46/min.

Key investigations included a complete blood count, which was within normal limits, and an arterial blood gas analysis, which was consistent with moderately severe anaemia and respiratory acidosis.

His blood alcohol level was 201 mg/dL, and his drug screen was negative for all substances except amyl nitrite.

He was treated with methylene blue, which was given intravenously at a dose of 20 mg/kg over 10 minutes and repeated every hour as necessary.

On completion of this treatment, his methaemoglobin level was reduced to 10%, and he was discharged from hospital the following day with no sequelae.

Key words: amyl nitrate, methaemoglobinemia, methylene blue

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auscultation. His systolic blood pressure was 70 mmHg, and his pulse was 60 beats min⁻¹. He was unresponsive to pain, and his pupils were constricted, equal and fixed.

Arterial and venous samples were drawn for arterial blood gas (ABG) analysis, MetHb, full blood count (FBC), and determination of electrolytes, urea and creatinine levels.

However, 12 min after arrival the patient suffered a bradyarrhythmic arrest, requiring cardio-pulmonary resuscitation and 2 mg adrenaline, administered intravenously. He regained a cardiac output after 30 s. The patient’s MetHb level was 94% (n<1.5%) and he was given 80 mg (c.1 mg kg⁻¹) of tetramethylthionine (methylene blue) intravenously over a period of 10 min. Twenty minutes after administration of the methylene blue, the patient’s colour had improved slightly and there was a return of spontaneous respiration, but he remained unresponsive to pain.

Further physical examination revealed a core temperature of 32.5°C (per rectum). There were no focal neurological signs, and the systolic blood pressure remained low (70 mmHg). The abdomen was soft and not distended. There was no sign of trauma, and no other abnormality was found.

The results of initial investigations were as follows (ranges in parenthesis): ABG (FiO₂=1) pH 7.17, (7.35-7.45); Pco₂, unable to be measured due to technical problems; Pcvo₂, 39 mmHg (32-45); HCO₃⁻, 14 mmol L⁻¹ (24-31); and base excess (B.E.) -14 (-3+3). Chest radiograph was normal. A 12-lead electrocardiograph showed sinus rhythm, rate 98 beats min⁻¹ with ST elevation (concave down) in leads V1-V6. Hb was 13.1 g dL⁻¹ (13.0-18.0), WCC was 9.7 x 10⁹ L⁻¹ (4.0-11.0), and platelet count was 211 x 10⁹ (150-400). Blood alcohol level was 0.15%.

A repeat MetHb measurement gave a value of 26%. The patient was given another 100 mg of methylene blue at this time. A further 50 mL of 8.4% sodium bicarbonate were administered for a persisting metabolic acidosis (pH, 7.05; Pco₂, 46; Pco₂, could not be measured; HCO₃⁻, 13; B.E., -19).

By 06.00 hours, the patient’s colour was pink. A repeat MetHb level was 1.6% at 09.30 hours. At this time the patient was opening his eyes to speech and obeying commands. He continued to improve and was extubated at 18.00 hours. He was confused initially, but his sensorium had cleared by the next morning. He remembered no details from the night of his overdose. Thirty-six hours after admission he was transferred from the intensive therapy unit to the ward.

It was decided to keep the patient in hospital and monitor him for haemolytic anaemia. However, the patient discharged himself, against medical advice, on day 5. There was no evidence of anaemia at this time, and he showed no evidence of any residual neurological deficit on clinical testing. Total creatinine phosphokinase (CPK) levels 12 and 36 h after admission were 385 and 681 U L⁻¹, respectively (<130 U L⁻¹). The MB fractions at these times were 24 and 25U L⁻¹, respectively (<15 U L⁻¹). A repeat ECG before discharge was normal. Clinically, the patient had made a complete, uncomplicated recovery. Further follow-up was performed by the patient’s local medical officer. The patient refused counselling from the drug and alcohol service.

We note that the patient presented again to our Emergency Department 6 months later with chest pain after injecting cocaine intravenously. ECG on this occasion was normal, and he was discharged for follow-up with his local medical officer.

DISCUSSION

Although rare, it is important to diagnose methaemoglobinaemia when it presents because it is potentially fatal and yet readily treated. A clue to the diagnosis is the appearance of chocolate brown blood upon venesection or arterial sampling. The diagnosis can be confirmed by spectrophotometric analysis of the patient’s blood, giving a MetHb level expressed as a percentage of the total Hb level. The blood should be analysed very soon after being drawn, as the MetHb level in the sample will decrease with time.

Aetiology

Table 1 lists the agents that most commonly cause acquired methaemoglobinaemia. It has been reported that ingestion of nitrates is not dangerous because they are degraded in the GIT. However, there are many case reports of severe, sometimes fatal, methaemoglobinaemia resulting from ingestion of isobutyl nitrite.

Management of acquired methaemoglobinaemia

After ensuring and protecting the airway, providing appropriate respiratory and cardiovascular support and decontamination (e.g., removing soiled clothing or decontaminating oxidants in the gut), tetramethylthionine (methylene blue, MB) should
Table 1. Agents most commonly implicated in acquired methaemoglobinaemia

<table>
<thead>
<tr>
<th>Category</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrates, nitrates</td>
<td>Isobutyl (amyl) nitrite</td>
</tr>
<tr>
<td></td>
<td>Glyceryl trinitrate (sublingual, i.v.)</td>
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<tr>
<td></td>
<td>Food/water contaminants</td>
</tr>
<tr>
<td>Local anaesthetics</td>
<td>Topical</td>
</tr>
<tr>
<td></td>
<td>Intravenous9</td>
</tr>
<tr>
<td></td>
<td>Benzocaine, prilocaine and lignocaine most commonly</td>
</tr>
<tr>
<td>Aniline dyes</td>
<td>Industrial11</td>
</tr>
<tr>
<td></td>
<td>Domestic products</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td></td>
<td>Dapsone (high dose)</td>
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<td></td>
<td>Quinones33</td>
</tr>
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be used early on if it is indicated. Figure 1 shows its mechanism of action.

Accepted indications for MB are a MetHb level of >30 - 40%, or a situation where the patient is symptomatic or anaemic, regardless of the MetHb level.24 The clinician must be careful to treat each case individually according to the clinical indicators of severity (e.g., level of consciousness, dyspnoea, myocardial ischaemia), as some patients have died16 or have been severely symptomatic17 with MetHb levels under 35%, while other patients have recovered with levels above 80%.14,18 The initial dose is 1 - 2 mg kg⁻¹ body weight, administered intravenously over 5 min.2,4,9 Significant clinical improvement and a substantial reduction in the MetHb level usually occur within 30 - 60 min. In cases where repeat doses of MB are required, concern may be caused by the fact that MB itself has a direct oxidant effect on Hb.8 This effect is likely to be more marked in the following conditions:

1. NADPH methaemoglobin reductase deficiency (see Fig. 1);
2. G6PD deficiency;
3. large doses of MB (> 7 mg kg⁻¹).

If a patient has a known deficiency of one of the above enzymes, or there is failure of an adequate dose of MB (up to 7 mg kg⁻¹) to reduce the MetHb level and produce a clinical improvement,34-36 then alternative or additional treatment with an exchange transfusion should be considered. Apart from the above situations, MB should not be withheld if the indications for its use and reuse are present. This is because the methaemoglobin-producing effects of MB in vivo are small,10,11 and are dominated by the methaemoglobin-reducing effects. Table 2 lists the reasons why acquired methaemoglobinaemia may fail to respond to MB.

Methylene blue, especially at doses of 7 mg kg⁻¹, may cause a sensation of dyspnoea, pressure on the chest, restlessness, excitation, apprehension, a feeling of impending death, tremor, nausea and vomiting.34 Persistent cyanosis after treatment of acquired methamoglobinaemia with MB may be due to an insufficient dose of methylene blue, failure to respond to methylene blue (Table 2), or blue discoloration of the skin and mucous membranes caused by the methylene blue itself. The latter may occur, despite the correction of methaemoglobinaemia.12 Thus a repeat MetHb level should be obtained before readministering methylene blue.

Table 2. Reasons for failure of methaemoglobinaemia to respond to methylene blue

| 1.   | G6PD deficiency |
| 2.   | NADPH reductase deficiency |
| 3.   | Sulphaemoglobinaemia |
| 4.   | Continued absorption of oxidant compounds |
R.J. Edwards et al. simply because the patient is still ‘blue’.

Use of pulse oximetry

Both the condition and the cure cause aberrations in pulse oximetry. Because MB absorbs light at a peak of 668 nm, a similar wavelength to reduced HB, MB is mistaken for reduced Hb by the oximeter, thus giving a spuriously low result for oxygen saturation.13 Methaemoglobin, which has a maximal light absorption at a wavelength similar to oxyhaemoglobin, 660 nm, is therefore mistaken for oxyhaemoglobin and oximeter overestimates oxygen saturation.15

Exchange transfusion

Exchange transfusion has been used to treat the acquired of methaemoglobinaemia both in children18,35,37–39 and in adults.32,36,40 Exchange transfusion is of therapeutic benefit where acquired methaemoglobinaemia has failed to respond to MB (see Table 2),35,36 where the clinical condition is so severe that additional treatment to MB may be helpful,18,40 or where the recommended dose of MB has been reached and the patient still has significant methaemoglobinaemia.32

REFERENCES

Extreme methaemoglobinemia by topical benzocaine and lignocaine. Archives of Internal Medicine 140, 1508–1509.


