CASE REPORT

An unusual cause of cyanosis in a patient with COPD

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SUMMARY

We present a case of acquired methaemoglobinaemia related to the prolonged use of dapsone in a patient with chronic hypoxia. The patient was initially successfully treated for infective exacerbation of chronic obstructive pulmonary disease (COPD). However, he remained persistently hypoxic on pulse oximetry despite a normal PaO₂ on arterial blood gas sampling. His fraction of methaemoglobin (FMetHb) was found to be elevated at 13%. After cessation of dapsone, his clinical cyanosis recuperated, his exercise tolerance and functional capacity improved and his FMetHb normalised to 1%.

were normal. Auscultation of the chest revealed mild bi-basal crackles without wheeze.

INVESTIGATIONS**Initial investigations**

Arterial blood gases (on 4 l/min O₂): pH 7.46, PCO₂ 4.46 kPa, PO₂ 8.02 kPa HCO₃ 24.3 mmol/l, SaO₂ 88.2%.

Blood profiling: haemoglobin 10.5 g/dl, white blood cell count 9.1×10^9 /l, C reactive protein 125.5 mg/l.

Plain chest radiograph showed patchy left-sided pneumonic changes consistent with infection on a background of hyper-inflated lungs.

BACKGROUND

This case demonstrates how mild methaemoglobinaemia can lead to a clinical decline in a patient known to have chronic hypoxia from chronic obstructive pulmonary disease (COPD). Failure to identify more unusual causes of hypoxia and cyanosis may lead to unnecessary investigations and missed opportunities for an early treatment.

CASE PRESENTATION

A 57-year-old man presented to hospital with a 2-week history of gradually increasing breathlessness and decreased exercise tolerance. He suffered from COPD (GOLD Grade II) and coeliac disease with coexisting dermatitis herpetiformis. Preadmission treatment with oral steroids and antibiotics had failed to improve his symptoms.

Physical examination demonstrated the patient to be peripherally cyanosed (peripheral oxygen saturation, SpO₂ 85% on 4 l/min of O₂) and tachypnoeic (20 bpm). His blood pressure and pulse rate

TREATMENT**Initial management**

Treatment of infective exacerbation of COPD was started with flow-controlled oxygen, intravenous antibiotics, nebulised bronchodilators and corticosteroids. Despite significantly improved inflammatory markers and clinical symptoms, the patient remained cyanosed and persistently hypoxic on pulse oximetry. Further arterial blood investigations with the patient breathing ambient air revealed a 'saturation gap' with a discrepancy between his measured peripheral oxygen saturation (SpO₂) and calculated haemoglobin oxygen saturation (SaO₂): pH 7.44, PCO₂ 5.37 kPa, PO₂ 7.77 kPa, HCO₃ 27.1 mmol/l, SaO₂ 86.4%, SpO₂ 79%. Co-oximetry was performed to determine the presence of dyshaemoglobins and revealed a significantly raised fraction of methaemoglobin (FMetHb) level of 13%.

The patient had been taking dapsone for dermatitis herpetiformis since 2006. A baseline FMetHb level of 1.5% at the start of treatment had gradually increased over time (table 1).

Table 1 Serial arterial blood gases with co-oximetric measurement of fraction of methaemoglobin level (FMetHb), fraction of inspired oxygen (FiO₂), pulse oximetry (SpO₂) and alveolar-arteriolar oxygen gradient (A-a O₂ gradient)

Parameters with normal range	Prior to starting dapsone 2006	2007	2009	2010	Current admission Feb 2012	After stopping dapsone Mar 2012
pH (7.35–7.45)	7.37	7.37	7.40	7.42	7.44	7.43
PCO ₂ (4.30–6.40 kPa)	5.26	5.39	5.28	4.69	5.37	4.89
PO ₂ (11.1–14.4 kPa)	9.21	9.49	9.89	13.7	7.77	8.86
SaO ₂ (95.0–99.0%)	92.0	91.3	92.6	96.1	86.4	91.1
FO ₂ Hb (94.0–98.0%)	89.8	81.8	85.7	88.1	74.7	88.9
FiO ₂ (%)	21.0	21.0	21.0	21.0	21.0	21.0
SpO ₂ (%)	92.0	91.0	94.0	94.0	79.0	94.0
A-a O ₂ Gradient (kPa)	4.2	3.7	3.5	0.4	5.5	5
FMetHb (0.0–1.5%)	1.5	6.5	5.1	8.1	13.0	1.0

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Figure 1 (A) Normal oxyhaemoglobin dissociation curve. Blue line for PCO_2 40 mm Hg, pH 7.40 and blood temperature 37°C ; PCO_2 partial pressure of carbon dioxide; H^+ hydrogen ion; MetHb methaemoglobin level. (B) Effect of methaemoglobinaemia on the oxyhaemoglobin dissociation curve. Arterial (a) and mixed venous (v) values shown, the O_2 content is given for normal blood, assuming a haemoglobin concentration of 150 g/L. Graphics adapted from Ole H Petersen, Lecture Notes: Human Physiology, Blackwell Publishing 2007.

A diagnosis of acquired methaemoglobinemia secondary to the dapsone therapy was thus considered. The implicated drug was stopped and replaced with topical mometasone furoate with advice from the dermatologist.

OUTCOME AND FOLLOW-UP

He was successfully discharged from hospital a week later once clinically stable. One month after cessation of dapsone, the patient was no longer cyanosed, achieving a peripheral oxygen saturation of 93% breathing room air and had a low-normal PO_2 on an arterial blood gas sampling. By that time, the FMetHb level had fallen significantly to 1%. Since then, his functional status has continued to improve and he remains active and independent without requiring supplemental oxygen.

DISCUSSION

Methaemoglobinaemia results from the formation and persistence of methaemoglobins in the circulation. Methaemoglobin is formed when ferrous ions (Fe^{2+}) within the haeme moiety are oxidised to ferric ions (Fe^{3+}) which are incapable of binding oxygen molecules. Moreover, their presence strengthens the oxygen-binding affinity of the remaining ferrous haemes within the haemoglobin tetramer, impairing their ability to unload oxygen to tissues. As normal reduction pathways become overwhelmed, methaemoglobins accumulate and cause a left-ward shift of the oxygen dissociation curve in keeping with the development of a state-of-functional anaemia¹ (figure 1). It is noteworthy that our patient's methaemoglobinaemia fluctuated at a low level before acutely rising in the context of a severe infective exacerbation of his underlying airways disease. The cause for this is likely to be multifactorial. Thromboxane and prostaglandin synthesis in response to infection increases oxidative stress on erythrocytes, as does dehydration. Normal ageing mechanisms also confer oxidative stress on erythrocytes which may contribute to an increase in methaemoglobin synthesis over the 6-year period.² Anaemia likely sensitised our patient to symptoms of methaemoglobinemia because of his lower functional haemoglobin reserve.

Causes of methaemoglobinaemia can be either congenital or more commonly, acquired. Infantile causes (4 months and younger) usually relate to underdeveloped protective cellular mechanisms. Common causes of acquired methaemoglobinaemia include agents which inflict a significant oxidant stress on cells. These include drugs such as lidocaine, benzocaine, amyl nitrite, sulfonamides and chloroquine as well as many environmental agents. Dapsone is particularly potent because of its pro-oxidant metabolite hydroxylamine which has a long half-life.^{3,4}

A methaemoglobin level of around 1% is deemed physiological. In a healthy individual, cyanosis develops when FMetHb levels reach 15–20% and symptoms ensue with levels of 25–50%. However, patients with a coexisting impairment in oxygenation may develop clinical features including cyanosis with only a modest elevation of the FMetHb level. While headache, dyspnoea, lightheadedness, weakness and confusion are reported in mild methaemoglobinaemia, individuals with more severe disease are at risk of cardiac arrhythmias, seizures and coma. Methaemoglobinaemia should be suspected in the presence of cyanosis and a saturation gap (disparity) between SpO_2 and SpO_2 .⁵

Treatment of methaemoglobinaemia depends on the severity of the condition. In asymptomatic patients with a methaemoglobin level of less than 20%, simple measures such as discontinuing the offending agent may be all that is required. In symptomatic patients or where the methaemoglobin level exceeds 20%, administration of supplemental oxygen and methylene blue may be indicated. Methylene blue promotes the enzymatic reduction of methaemoglobin by NADPH-methaemoglobin reductase, thereby re-establishing the Fe^{2+} state. In severe cases of shock, blood transfusion may be required.⁶

This case demonstrates how mild methaemoglobinaemia can lead to a clinical decline in a patient known to have chronic hypoxia from COPD. There are no known similar published cases in English word. Failure to identify more unusual causes of hypoxia and cyanosis may lead to unnecessary investigations and missed opportunities for an early treatment. Specific consideration is warranted when patients with chronic respiratory disease are started on agents capable of inducing methaemoglobinaemia. Pharmaco-clinical vigilance may help prevent the risk of such patients developing this potential complication.

Learning points

- Failure to identify more unusual causes of hypoxia may lead missed opportunities for earlier intervention.
- Causes of methaemoglobinaemia can be either congenital or more commonly, acquired.
- Common causes of acquired methaemoglobinaemia include agents which inflict a significant oxidant stress on cells.
- Patients with a coexisting impairment in oxygenation may develop clinical features including cyanosis with only a modest elevation of the fraction of methaemoglobin level.

Competing interests None.

Patient consent Obtained.

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