Methaemoglobinaemia: a case of mistaken identity

Acute methaemoglobinaemia is an uncommon, treatable disorder in which the iron atom in the haem moiety of haemoglobin A is oxidized. Methaemoglobin cannot bind oxygen and oxygen delivery to the tissues may be low despite normal, or even raised, arterial PO_2 (PaO_2), haemoglobin concentration and cardiac output. Central cyanosis and low haemoglobin saturation on pulse oximetry may mislead the clinician to look for a cause for presumed arterial hypoxaemia, which will delay the diagnosis of methaemoglobinaemia, and risk inappropriate investigations and treatment.

This article presents a case report in which the diagnosis of methaemoglobinaemia was delayed because of misinterpretation of the clinical data, and explains the principles underlying pulse oximetry and the potential for errors when relying solely on the information obtained using it.

Case Report

A 69-year-old man was admitted under the care of the orthopaedic surgeons after fracturing his femur. He had been diagnosed with polyarteritis nodosa 10 years previously and was asthmatic. A recent echocardiogram had revealed moderate aortic stenosis. His medications were dapsone 250 mg daily, prednisolone 5 mg daily, salbutamol and beclomethasone inhalers. The planned orthopaedic management was open reduction and internal fixation.

He had no complaints apart from the pain associated with his injury. He did not complain of breathlessness or chest pain. He was alert and orientated; heart rate 80/minute and regular; arterial pressure 132/74 mmHg; respiratory rate 16/minute; his chest was clinically clear. However, his lips were blue and pulse oximetry was 79% with a good waveform. A differential diagnosis of pulmonary or fat embolism was made and high flow oxygen was given. Further investigations were ordered and a medical opinion sought from a chest physician.

Laboratory haemoglobin was 105 g/litre; a chest X-ray showed chronic pleural thickening but no acute lung changes; an electrocardiogram confirmed normal sinus rhythm. Arterial blood analysis (breathing oxygen 15 litres/min from a face mask with attached reservoir bag) showed PaO_2 23 kPa, $PaCO_2$ 4.5 kPa, pH 7.42, bicarbonate 24 mmol/litre, base excess zero. The chest physician agreed with the diagnosis of acute thrombotic pulmonary embolism and the patient was heparinised pending further investigation by computed tomography pulmonary angiography. This showed minor atelectasis, bronchiectasis and chronic pleural thickening consistent with previous asbestos exposure but no evidence of pulmonary embolism or parenchymal lung disease.

The patient was referred for an anaesthetic opinion before the proposed surgery, and the raised PaO_2 was noted. As the patient was clinically well and all investigations were negative, he was deemed fit for urgent surgery under general anaesthesia.

In the anaesthetic room routine monitoring was attached. Again, a low peripheral oxygen saturation (approximately 86%) was observed on pulse oximetry breathing air. After routine induction of general anaesthesia, the low saturation persisted despite ventilation of the patient's lungs with 100% oxygen. At this point, a diagnosis of acquired methaemoglobinaemia – secondary to dapsone therapy – was considered. Methylene blue 20 mg was injected intravenously slowly and the pulse oximetry reading increased from 86 to 96% within a few minutes. The rest of the anaesthetic was uneventful.

Postoperatively he was transferred to the high dependency unit for observation and started on ascorbic acid. He had a methaemoglobin concentration of 4.8% (normal range 0–2%) even after the methylene blue and return to normal peripheral oxygen saturation. His dapsone was not restarted. Further investigation confirmed normal red cell methaemoglobin reductase concentration and a diagnosis of acquired methaemoglobinaemia secondary to dapsone therapy.

Discussion

Most (98%) of the oxygen in blood is bound to haemoglobin and only 2% is dissolved in plasma. Normal haemoglobin A is a tetramer of two α and two β subunits. Each subunit is attached to a porphyrin haem iron moiety which reversibly binds oxygen as long as the haem iron is in its normal physiological ferrous (Fe^{2+}) state. The binding of oxygen by haemoglobin exhibits positive cooperativity, i.e. binding of an oxygen molecule to the first haem increases the affinity of a second oxygen to the second haem, and so on. The resulting oxygen dissociation curve for haemoglobin is sigmoid. It is important to note that once haemoglobin is fully saturated (PaO_2 ~ 13 kPa), little additional oxygen is transported in the blood even with large increases in PaO_2. Conversely, once the saturation decreases below approximately 90% (PaO_2 ~ 8 kPa), a small decrease in PaO_2 causes a large reduction in saturation.

In haemoglobinopathies, haemoglobin A synthesis is reduced or replaced by abnormal forms of haemoglobin. They may be genetic or acquired and include the thalassaemias, sickle cell disease, carboxyhaemoglobinaemia (carbon monoxide poisoning) and sulphhaemoglobinaemia (caused by sulphonamides). They all cause reduced oxygen transport despite normal cardiorespiratory function.

In methaemoglobinaemia, the normal ferrous (Fe^{2+}) form of iron is converted by metabolic and toxic oxidative stresses to the ferric (Fe^{3+}) form, which cannot bind oxygen. Methaemoglobin is present in healthy people as a result of endogenous oxidation but circulating concentrations are normally below 1% because of erythrocytic enzyme action by cytochromic NADH methaemoglobin reductase. Clinically significant methaemoglobinaemia develops as a result of congenital deficiency of the reductive enzymatic pathways or overwhelming oxidative stress, e.g.

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exposure to oxidizing agents, such as dapsone, nitrites, nitrates and prilocaine. Methaemoglobin concentrations above 20% cause malaise, dyspnoea, headache, vomiting, syncope and death.

Treatment of mild methaemoglobinaemia is by oxygen therapy, symptomatic support and withdrawal or elimination of the precipitating agent. Methaemoglobin has a half life of about 1 hour provided that endogenous reductase activity is normal. More severe cases require intravenous injection of a potent electron donor such as methylene blue. The threshold for giving methylene blue is a methaemoglobin concentration more than about 20% in symptomatic cases and 30% in asymptomatic cases. The recommended dose is 1–2 mg/kg over 5 minutes, after which methaemoglobin concentrations approach the normal range within 1–2 hours. The total dose should not exceed 7 mg/kg. Doses in excess of 15 mg/kg may cause paradoxical methaemoglobinaemia. Methylene blue activates an alternative reducing enzyme pathway via one of its metabolites, leukomethylene blue. In the treatment of mild congenital methaemoglobinaemia, ascorbic acid is the antioxidant normally used.

Spectrophotometry is commonly used to assess oxygenation, and the commonest application is the pulse oximeter, which has become ubiquitous. It is easy to use, non-invasive and provides rapid information on the oxygenation of arterial blood and the adequacy of the peripheral circulation. Spectrophotometry is based on the principle that fluids absorb light proportionally to solute concentration. A beam of light of specific wavelength is transmitted across a medium containing the solute of interest and the intensity of the transmitted light is measured by a photodetector.

Normally, the two main forms of haemoglobin in the circulation are oxygenated and deoxygenated haemoglobin A. The absorption spectra of these two forms differ (*Figure 1*). Almost all pulse oximeters currently available use light at two different wavelengths (660 nm and 940 nm), from which the proportion of the two forms can be estimated. Using a complex algorithm, the pulse oximeter subtracts the non-pulsatile component resulting from blood in capillaries and veins, ensuring that the reading obtained represents the saturation of arterial blood – which is only 5% of the total colour 'signal' in the blood.

The reliability of pulse oximetry is entirely dependent on the assumption that the only forms of haemoglobin present are oxygenated and deoxygenated haemoglobin A, an approximation that is usually satisfactory for routine clinical use. However, if the circulation contains significant levels of abnormal forms of haemoglobin, pulse oximetry readings may be unreliable. Inaccurate readings may also be obtained in other circumstances (Ralston et al, 1991a,b; Webb et al, 1991). *Table 1* summarizes potential sources of error.

Methaemoglobin absorbs light almost equally at the two wavelengths used in standard pulse oximetry. This absorbance ratio of one is the same as normal haemoglobin A that is 85% saturated with oxygen. This is why a pulse oximeter tends towards 85% as the proportion of methaemoglobin increases, independently of the PaO_2.

Co-oximeters are the most accurate instruments for measuring oxygen saturation, but they are complex, expensive laboratory instruments. They measure absorbance at many wavelengths and thus can provide information on the type and proportion of all forms of haemoglobin present. More complex pulse oximeters that use many wavelengths are just coming onto the market, and are able to diagnose methaemoglobinaemia and carboxyhaemoglobinaemia (Barker et al, 2006), but it will be some time before these are generally available.

The initial abnormal feature in this case was cyanosis with a low pulse oximeter reading. Initially, giving high flow oxygen was appropriate. However, the arterial blood gas analysis was misinterpreted. The high PaO_2 should have led to a re-evaluation of the diagnosis of pulmonary embolism, particularly as the patient was asymptomatic. An abnormally low peripheral oxygen saturation cannot be interpreted without knowing the PaO_2. A discrepancy between the two requires co-oximetric blood gas analysis to look for haemoglobinopathies. If this had happened in this case, the diagnosis would have been made preoperatively and before unnecessary investigation and treatment was undertaken. BJHM

Figure 1. Absorption spectra for oxy- and deoxyhaemoglobin.

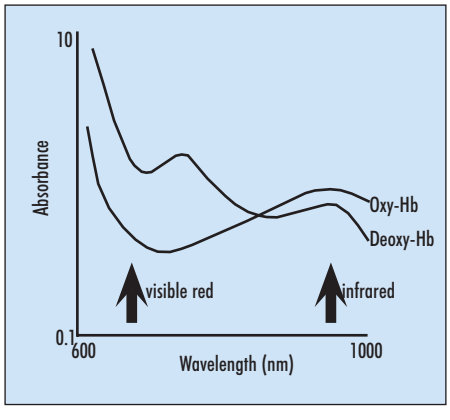

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Table 1. Sources of error in pulse oximetry

Source	Effect on pulse oximetry
External bright lighting	False low reading
Nail varnish	False low reading
Venous congestion	False low reading
Methaemoglobinaemia	Tendency towards 85% saturation independent of PaO_2
Carboxy-haemoglobinaemia	False high reading
Poor peripheral perfusion	Failure to acquire signal
Electrical diathermy	Interference with signal
Shivering	Interference with signal
Malpositioned probe	Inaccurate
Use of pulse oximeter outside calibration range (70–100%)	Inaccurate
Pulse oximetry is not affected by fetal haemoglobin, sulphhaemoglobin, bilirubin or pigmented skin	