Investigation vignette

Unexplained Respiratory Distress and Desaturation

CASE REPORT

The patient was a 52 year old man who had presented with septic shock and an acute abdomen, after a prolonged illness for which he had not sought treatment. At laparotomy there was little to find except a mildly inflamed appendix. His post-operative course in the intensive care unit (ICU) was complicated by multiple organ failure: septic shock, acute lung injury, anuric renal failure, coagulopathy, hepatic failure and encephalopathy. The relatively rare diagnosis of disseminated toxoplasmosis was confirmed from tissue specimens of appendix, skin and lung. He also tested positive for the Human Immunodefiency Virus (HIV) and was found to have a CD_4 count of zero. Pyrimethamine, clindamycin, and cotrimoxazole were commenced to treat the toxoplasmosis. Empiric therapy of ganciclovir, and amphotericin B was also commenced. Screening was done for other AIDS-associated illnesses.

He was subsequently found to have no evidence of pneumocystis carinii (PCP) or cytomegalovirus infection. A secondary diagnosis of disseminated Mycobacterium Avium Complex (MAC) infection was made after a bone marrow biopsy, and treatment with azithromycin and ethamutol was added. Severe pancytopenia progressed and was thought to be due to marrow suppression due to MAC infection and exacerbated by the large doses of cotrimoxazole. Dapsone was substituted for the cotrimoxazole.

After three weeks the respiratory failure, encephalopathy and profound muscle weakness had resolved enough to consider a trial of extubation. The first attempts at T-piece weaning were abandoned because of increasing anxiety and tachypnoea, despite objective evidence that would predict success. He was compliant, strong, had a good cough with minimal sputum and his chest X-ray had only subtle interstitial markings. His ventilator settings were stable with a Positive End Expiratory Pressure (PEEP) of 5 cmH_2O, and pressure support of 8 cmH_2O and an unsupported FVC of 1.6 litres. Arterial blood gas analysis on an F_IO_2 of 0.28 showed a PaO_2 of 75 mmHg. He could not articulate why he felt restless or became tachypnoeic during attempts at weaning.

The nursing staff and medical staff had become used to ignoring his pulse oximetry readings as the pulse oximeter was continually 'misreading'. They had begun relying predominantly on the PO_2 and the SO_2 from arterial blood gas printouts. They were reassured by the occasional appearance of readings of 99% when the oximetry probe was repositioned. Co-oximetry of the arterial blood gas as shown in figure 1 provides the reason for the failure to wean.

Name	Age	Sex
Mr. A. B.	52	M

PO_2	75	mmHg	(80 - 105)
PCO_2	45	mmHg	(35 - 45)
pH	7.46		(7.35 - 7.45)
Calculated HCO_3^-	31	mmol/L	(21 - 28)
BE	6.9	mmol/L	(-3 - 3)
ctHb	65	g/L	(115 - 160)
SaO_2	95	%	(94 - 99)
FO_2Hb	76	%	(96 - 99)
FCOHb	0.3	%	(< 2)
FMetHb	20.5	%	(0 - 2)

Figure 1. Arterial blood gas

Diagnosis: Methaemoglobinaemia of more than 20% caused by dapsone.

Methaemoglobinaemia is rarely encountered as a clinical problem. Symptoms are described as unlikely with levels of less than 15% in healthy people although 'cyanosis' may be noted. Cyanosis in methaemoglobinaemia is clinically detectable when the absolute concentration of methemoglobin exceeds 15 g/L, equivalent to 8 - 12% methemoglobin levels. In contrast, cyanosis due to de-oxygenated haemoglobin may not be noted until the total reduced haemoglobin is 40 to 50 g/L.[1] Case reports describe respiratory distress with levels of 20 - 45% and impaired consciousness with levels above 45%. Although survival has been described with levels of 80%, this is considered a lethal degree of methaemoglobinaemia.[2]

Methaemoglobin is an altered form of haemoglobin in which the ferrous (Fe^{2}+) irons of heme are oxidized to the ferric (Fe^{3}+) state. The ferric haem molecules of methaemoglobin are unable to bind oxygen. In addition, the oxygen affinity of any associated ferrous haems in the haemoglobin tetramer is increased. Hence oxygen unloading to the tissues is impaired. Hence a 20% methaemoglobin level is more detrimental than merely having a 20% effective reduction in circulating haemoglobin. This might not bother a young person abusing amyl nitrate 'poppers' to excess, but a deconditioned man recovering from multiple organ failures with a baseline haemoglobin of 70 g/L may decompensate when the effective available haemoglobin is markedly reduced.

During the formation of oxyhaemoglobin from deoxyhaemoglobin and molecular O_2, one electron is partially transferred from the iron in haem to the bound oxygen, forming a ferric-superoxide anion complex (Fe^{3+}▪O_2^-). During deoxygenation, most of the oxygen leaves the molecule as molecular oxygen, but a small amount leaves as a superoxide (O_2^-) radical. Under the latter circumstance, the partially transferred electron is not returned to the iron moiety, leaving the iron in the ferric state (Fe^{2+}) and forming methaemoglobin. Auto-oxidation of haemoglobin occurs spontaneously *in vivo* at a slow rate, converting 0.5 - 3 % of available haemoglobin to methemoglobin per day to maintain a steady-state level of methaemoglobin of about 1% of total haemoglobin.[1]

Methaemoglobin is also formed from the oxidation of the iron in haem via reactions with free radicals and endogenous compounds, including hydrogen peroxide (H_2O_2), nitric oxide (NO) and hydroxyl radical (▪OH^-). Exogenous compounds may oxidise haemoglobin to methaemoglobin directly, by means of a metabolic derivative or by generating such free radicals during their metabolism. This is the proposed mechanism with dapsone.

Methaemoglobinaemia may be acquired through the action of a variety of drugs, toxins and foodstuffs or may be caused by an inborn defect in haemoglobin structure or red cell metabolism.[2,3] The commonest drugs implicated are prilocaine, anti-malarials, dapsone, sulphonamides and dyes (including methylene blue). Foodstuffs may contain high levels of nitates as a preservative. To diagnose a genetic predisposition, blood can be tested for methaemoglobin reductase activity assay, but in most cases a careful drug history reveals the cause. Most cases of hereditary methaemoglobinemia are due to a deficiency of cytochrome b5 reductase.[4]

Some of the diagnostic confusion in our case may have arisen from the disparity in the techniques available to assess oxygen saturation. Currently, we regularly use three methods: bedside absorption pulse oximetry (SpO_2), the arterial blood gas analyser calculated SO_2, and co-oximetry.

Absorption (or reflectance) pulse oximetry uses the Beer-Lambert principle: where two wavelengths of light (red light at 660 nm and infra-red light at 940 nm) are emitted and subsequently measured. Software subtracts non-pulsatile (background and end-diastolic) data leaving a pulsatile, peak systolic absorption pattern, where the differing proportions of 660 nm light (absorbed by deoxyhaemoglobin) and 960 nm light (adsorbed by oxyhaemoglobin) are measured. Using the Beer-Lambert principle the ratio R is calculated using the formula:

$$R = (AC_{660}/DC_{660}) / (AC_{940}/DC_{940})$$

Where,

AC_{660} = *the absorbance of 660 nm light by the pulsatile or 'alternating' component*

DC_{660} = *the absorbance of 660 nm light by the continuous or 'direct' component.*

In the absence of dyshaemoglobin the ratio R is uniquely related to SaO_2. In practice R is plotted against a pulse oximeter calibration algorithm derived from experimental subjects and SpO_2 is presented in the readout.[5] Methaemoglobin has two absorption peaks, at 630 nm and 960 nm, and this results in similar absorptions of the transmitted light energies (a ratio of 1:1) which when plotted by the oximeter against the algorithm corresponds to an SpO_2 of 85%. This may give the false impression of some deoxyhaemoglobin when Hb is fully saturated, and similarly a false impression of some oxyhaemoglobin when there is a

deficit of it. With higher levels of methaemoglobin the oximeter will trend towards 85%.

The convention of SO_2 used by most blood gas analysers, including here the Bayer 865, represents a calculated 'saturation' of haemoglobin. A standard Severinghaus nomogram of Hb saturation is used to 'read off' a saturation corresponding to a given measured PaO_2. Again the nomogram was created using only deoxyhaemoglobin and oxyhaemoglobin.

The co-oximeter used in the blood gas analyser *measures* a number of wavelengths of light and their relative absorption by four haemoglobin species in the blood: carboxyhaemoglobin (500 nm), methaemoglobin, deoxyhaemoglobin and oxyhaemoglobin. The proportions are accurate to ± 1 % except when excessive proportions of methemoglobin (greater than 10%) are present, or a fifth or sixth haemoglobin species is present.[6]

The methaemoglobinaemia in this case was resolved by infusing 100 mg (2 mg/kg) methylene blue intravenously over an hour, and subsequently discontinuing the dapsone and adding ascorbic acid 1 gram per day. Clindamycin was substituted for the dapsone. After the methylene blue infusion the saturations by pulse oximetry increased from 87% to 98% on both bedside pulse oximeter and SO_2. The patient was subsequently weaned from the ventilator, commenced on oral antiretroviral therapy, discharged from ICU and eventually home after ninety nine days in hospital, with a CD_4 count of 0.05 $x10^9$/L.

In conclusion, significant methaemoglobinaemia is rarely encountered in Intensive Care. However, diagnosis could be delayed due to failure to appreciate the different techniques and conventions used to assess and describe haemoglobin saturation.

L. PRITCHARD
P. M. GARRETT
Department of Intensive Care, Nambour Hospital, Sunshine Coast, QUEENSLAND

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