Methaemoglobinaemia-induced oxygen desaturation complicating chest trauma

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Case presentation

A 72-year-old man presented to the Emergency Department by ambulance following a rollover motor vehicle crash preceded by black-out symptoms. He had been suffering from dermatitis herpetiformis for the last six years and was being treated with dapsone 100 mg and a partially gluten-free diet. On admission he had a respiratory rate of 22, pulse oximetry saturations of 89% improving to 93% with 3 l/min via nasal prongs, a heart rate of 75 bpm, and a non-invasive blood pressure of 111/52. No life-threatening injuries were identified on primary or secondary survey. A trauma CT-series noted left sided rib fractures. The patient was later transferred to the ward for observation with analgesia for chest wall tenderness.

On the ward, ongoing lethargy and confusion along with a fall in pulse oximetry from 90% to 85% when supplementary oxygen was removed was noted. Oxygenation, measured and monitored values noted during days 1 and 2 of admission are listed in **Table 1**. The patient deteriorated on day two of admission with worsening hypoxia, saturations measured by pulse oximetry (SpO2) were 91% despite 15 litres of oxygen via non-rebreather mask, and a non-invasive systolic pressure of 85 mmHg despite 2 litres of 0.9% normal saline intravenous therapy. A provisional diagnosis of pain-associated hypoventilation and atelectasis was made. The patient was transferred to the Intensive Care Unit (ICU) and commenced on high-flow nasal cannulae (HFNC) with a fraction of inspired oxygen (FiO2) of 0.6 with flows of 60 l/min. This produced an improvement in saturations (from 85% to 91%). A subsequent radiology review of imaging revealed a stable grade I splenic laceration. Supportive care was continued with non-operative management of the identified injuries.

Investigations revealed a haemoglobin of 103 g/l with an associated peripheral blood smear demonstrating "bite" and "blister" cells. Arterial blood gas (ABG) confirmed hypoxaemia with a partial pressure of oxygen (PaO2) of 80 on 15 l/min, improving to PaO2 of 192 with HFNC therapy with a FiO2 of 50%. A methaemoglobin fraction of 12% was noted and an arterial-oximetry to pulse-oximetry 'saturation gap' of 9% was recorded (**Table 1**).

A diagnosis of dapsone-induced methaemoglobinaemia alongside dapsone-induced oxidative haemolytic anaemia was made and the patient was commenced on ascorbic acid oral therapy (200 mg three times a day). Methylene blue was not used due to clinician concerns of precipitating further oxidative insult and haemolysis. The patient was stepped down from the ICU on day five with supplementary oxygen running at 4 l/min via nasal prongs and saturations of 94%. He was discharged home on day nine following a total of nine days of ascorbic acid therapy. Saturations at discharge were 98% on room air.

Case discussion

Hypoxaemia in chest trauma

The common causes of hypoxaemia in chest trauma are that of shunt, V/Q inequality, hypoventilation and dead space ventilation. These physiological entities may present and occur in combination as a result of a diverse form of pathologies, the most important of which are considered as the deadly dozen. The deadly dozen encompasses six immediately life threatening and six potentially life threatening chest injuries, which are that of 1) airway obstruction, 2) tension pneumothorax, 3) open pneumothorax, 4) massive

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haemothorax, 5) flail chest, 6) cardiac tamponade, 7) aortic injuries, 8) tracheo-bronchial injuries, 9) oesophageal injury, 10) diaphragmatic injury, 11) myocardial, and 12) pulmonary contusion. (1)

Pathological absolute shunt (perfusion through non-ventilated lung) may be considered when there is an increased difference between alveolar and arterial oxygen tension (PAO2-PaO2), which in normal health is only 4-6 mmHg. In trauma, this gradient may be profound owing to the effects of pulmonary contusion (and associated atelectasis, oedema, inflammation, and/or infection), pneumo and/or haemothorax. In these high shunt conditions, the non-ventilated alveolar units cannot provide an interface for any increased inspired fraction of oxygen, and there will be no increase in the PaO2. A PaO2/FiO2 calculation can provide an estimate of the amount of shunt - a ratio of >200 suggests a shunt of >20% where as a ratio of <200 suggests a shunt of less than 20%. (2)

In the setting of hypoventilation, which may occur due to head injury and decreased central respiratory drive, or pain with rib fractures and chest wall tenderness limiting voluntary respiration, hypoxemia may be remedied with an increase in the fraction of inspired oxygen.

In practice, there is often superimposition of associated V/Q mismatch, absolute shunt and hypoventilation owing to the effects of concomitant conditions such as contusion, oedema, atelectasis, pain and/or infection.

Dapsone and methaemoglobinaemia

Dapsone is uncommonly used as an antimicrobial in Australia or New Zealand, but occasionally used for various dermatological conditions including dermatitis herpetiformis and is increasingly used worldwide as a second line agent for Pneumocystis carinii prophylaxis or treatment in the immunocompromised where the patient is intolerant to sulfa drugs. (1,3,4)

Broadly, dapsone is an antibiotic of the sulfone class with utility as an anti-leprotic, antifungal and immune modulator agent. It exerts antimicrobial effect through enzymatic inhibition of folate synthesis leading to a bacteriostatic action. Dapsone has a 70% oral bioavailability and a volume of distribution of 1.5 l/kg, and is extensively hepatically metabolised via phase I and phase II metabolism and the drug undergoes entero-hepatic recirculation. The phase I hydroxylamine-metabolite is suspected to produce the adverse haematological effects of methaemoglobinaemia and oxidative haemolysis. (5) The elimination half-life is variably reported to be 10 to 80 hours. (4)

Methaemoglobin is transiently produced in normal physiology when the Fe2+ cation of the haeme molecule is auto-oxidated to Fe3+. The Fe3+ is unable to bind oxygen and further complicates haemoglobin carriage of oxygen by increasing the affinity, and limiting the tissue offloading, of normal oxy-haemoglobin. In normal health less than 1.5% of circulating haemoglobin is in the methaemoglobin state. Conversion back to the Fe2+ state occurs via two methods within the red blood cell. The most physiologically important pathway is via a nicotinamide adenine dinucleotide and hydrogen (NADH) dependent reduction catalysed by cytochrome b5 (**Figure 1**). A lesser active pathway also exists which utilises NADH and glucose-6-phosphate dehydrogenase in the hexose-monophosphate shunt, but requires an electron acceptor such as methylene blue or riboflavin to become activated. (6) Pathological methaemoglobinaemia may result from genetic abnormalities in the reduction pathways, such as in G6PD deficiency, type I and II cytochrome b5r deficiency, or in morphological abnormalities of haeme structure (HbM). (7) In addition, there are about forty pharmacological compounds that may overwhelm the normal oxidation-reduction balance of haeme and red blood cell metabolism to result in acquired methaemoglobinaemia. Frequently encountered methaemoglobin precipitating drugs and compounds are listed in **Table 2**. Dapsone is a major cause of drug induced methaemoglobinaemia. (8,9) The generation of methaemoglobin is thought to be dose dependent but there is an absence of clear dosing safety margins. (3) The majority of case reports pertaining to dapsone induced methaemoglobin are in the context of accidental ingestion (in paediatric populations or mistakenly taken as a drug of abuse), monopharmacy or polypharmacy overdoses, or due to inadvertent pharmacological interaction with other methaemoglobin inducing agents (**Table 2**). (10-13)

Clinically dapsone-induced methaemoglobin is suspected when an unexplained hypoxia arises per peripheral pulse oximetry with a tendency of saturations towards 85%. The described signs vary dependent on the level of methaemoglobinaemia. Cyanosis with discoloration of blood if observed observed at 15% to 20%. A methaemoglobin fraction between 20-45% is associated with dyspnoea, dizziness, lethargy and headaches. Significant neurological, metabolic and cardiovascular complications, including seizures, coma, acidosis and arrhythmia can be observed at

levels greater than 45%. Levels above 70% are associated with a high mortality. (4,11,13) Survival has been reported at levels of 83%. (14) Though the majority of those affected by met-haemoglobinaemia will not have adverse clinical consequences or require treatment, co-morbid conditions, such as respiratory or cardiac disease, may result in symptom presentation at lower levels. (4)

Dapsone may further impact the haematological system due to a dose dependent oxidative haemolytic anaemia. (15) Circulating red blood cells may be unable to clear oxidised proteins with pathological deposition onto the cell membrane. Characteristic bite cells are observed on a peripheral blood smear.

Other concerning significant adverse effects of dapsone use include that of the drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, sulfhemoglobinemia, liver impairment and peripheral neuropathy. (15)

Pulse oximetry and methaemoglobin

Digital pulse oximetry is an essential component of monitoring in anaesthesia and critical care medicine. It provides a non-invasive, indirect estimation of haemoglobin saturation to allow for rapid assessment for possible hypoxaemia. The equipment employs light emitting diodes, which alternately emit pulses of infra-red light at 660 and 940 nanometres at a rate of 100 Hertz. Deoxygenated haemoglobin has a higher absorbance of light (extinction coefficient) at 660 nm in comparison to oxygenated haemoglobin, which has a peak absorbance of light at 940 nm. Light, which is absorbed by the arterial inflow is calculated as a ratio to that, which is absorbed by the venous outflow and other tissues and this ratio is computed to provide a saturation.

The most commonly used digital pulse oximeters assess a functional saturation of oxy-haemoglobin to all other forms of haemoglobin. This does not account for other abnormal forms of haemoglobin, such as methaemoglobin, carbon-monoxy-hemoglobin and sulfhaemoglobin, which may be present in significant quality to produce a functional anaemia. These abnormal forms can only be readily monitored with fractional saturation.

The absorbance spectrum of methaemoglobin mimics that of oxy-haemoglobin and deoxy-haemoglobin with absorbance peaks of 630 and 960 nm (**Figure 2**). This drives the functional absorbance ratio of oxyhaemoglobin to deoxy-haemoglobin towards 1 which is computed by a conversion algorithm as a saturation of 85%. Therefore the saturations displayed are a weighted average of the available oxy-haemoglobin, deoxy-haemoglobin and the component of met-haemoglobin (which is 85%). The specific quantitative level of methaemoglobin cannot be accurately inferred from the peripheral saturations as the light absorbance reaches a plateau at levels of around 30% of methaemoglobin. (4,10) The oximetry waveform on monitoring remains unchanged provided that the peripheral circulation remains intact. (11)

A saturation gap is commonly noted whereby there is a greater than 5% difference between digital pulse oximetry and arterial blood gas saturation measurement. This arises as most arterial blood gas assessment of oxygen saturation is estimated per the directly measured PaO2 with correction for PaCO2, pH, followed by application to a standardized oxygen-haemoglobin dissociation curve. (10,11) Provided that oxygen transfer from the alveolus to the blood is not complicated by shunt, the PaO2 is typically higher than expected and increases in response to supplementary oxygen therapy but without clinical improvement in the patient.

Methaemoglobin is specifically measured as a percentage by multiple wavelength co-oximetry. This is most commonly conducted on a blood sample though peripheral spectroscopy monitors are becoming available. (16) An affected arterial blood sample is characteristically described as having a chocolate brown colour that does not turn red in light. (10)

In our case arterial blood gas analysis oximetry was measured on a Radiometer ABL 800 Flex device. The estimated oxygen saturation was indirectly calculated per the measurement of the PaO2 per an amperometric method and then correlated to the oxygen-haemoglobin dissociation curve. Methaemoglobin measurement was conducted via co-oximetry measuring absorbance at 128 wavelengths to differentiate between normal (oxygenated haemoglobin [FO2Hb] and deoxygenated haemoglobin [FHHb]) and abnormal (carboxyhaemoglobin [COHb] and met-haemohaemoglobin [MetHb]) species. (17,18) A saturation gap was noted when the difference between the peripheral pulse oximetry (SpO2) and arterial estimated oxygen saturation was greater than 5%.

Treatments for dapsone-induced met-haemoglobinaemia

Treatment of acute dapsone-induced met-

haemoglobinaemia is primarily with medications geared to enhance the activity of reductive pathways of methaemoglobin within the red blood cell. As with all toxicities and toxicological syndromes a step-wise approach should be considered with cessation of the offending drug, resuscitation, supportive care and investigation occurring alongside specific treatments. Methylene blue is an effective antidote that is advocated for use in methaemoglobinaemia when symptomatic hypoxia is present and the percentage of methaemoglobin is greater than 20%. (13) Methylene blue has a site of action within the red blood cell as a cofactor to the alternative pathway nicotinamide adenine dinucleotide phosphate and hydrogen (NADPH) methaemoglobin reductase and it is oxidized to generate leukomethylene blue which acts as an electron acceptor to reduce methaemoglobin. (6) The initial intravenous dose is 1-2 mg/kg which may be repeated every three to five minutes for up to thirty minutes. It can produce a rapid and meaningful drop in the methaemoglobin fraction within one hour but a rebound increase has been observed with use in dapsone-induced methaemoglobin. (13) The common side effects of administration are nausea, diarrhoea, dyspnoea and perspiration, but methylene blue does carry a significant adverse risk profile including precipitating a serotonin syndrome upon interaction with serotonergic drugs, increases in systemic and pulmonary vascular resistance, bluish discoloration of the skin and urine, momentary loss of the ability to accurately monitor saturations via pulse oximetry interference (lasting as long as 115 seconds), and, most concerning, an oxidative effect in which there may be paradoxical generation of methaemoglobin and haemolysis (albeit at higher total doses of 7-15 mg/kg). (13,19) Dextrose administration may be suitable in some patients to replenish NADPH via glycolysis within the erythrocyte. (4) Ascorbic acid is a reducing agent in many cellular reactions. It has been used to enhance the rate of methaemoglobin reduction in numerous case reports, however, the optimal dose and duration of therapy remains unclear and doses up to 30 mg/kg have been tried. It may be of particular value when there is concern of an underlying issue in normal cellular methaemoglobin reductive pathways, such as in glucose-6-phosphate dehydrogenase deficiency or in enhanced oxidative stress upon red blood cells. (12,13,20) Activated charcoal may be considered in acute ingestion or when there is a clinical suspicion of enterohepatic recirculation producing a rebound methaemoglobinaemia post dosing of medications aimed to support the reduction of methaemoglobin.

Concerns of chronic (and possible asymptomatic) dapsone-induced methaemoglobin generation may be managed by concomitant cimetidine administration. Cimetidine produces a cytochrome P450 mediated decrease in the production of damaging dapsone-hydroxylamine derivatives. (9)

Conclusion

Our case of chest trauma primarily complicated by rib fractures and pulmonary contusion with subsequent hypoventilation, atelectasis and shunt highlighted the need for a thorough assessment of expected pathophysiological factors, which may produce hypoxemia. In addition, our case demonstrated the need to assess the unique patient factors, which may be present and produce significant interference with measurement and monitoring of an unwell patient.

Methaemoglobinemia remains a diagnostic challenge as the precipitants may be surreptitious and collude with other therapies to impair oxygen delivery to tissues. In addition, bedside monitoring is traditionally limited and thorough assessment of arterial blood gas samples and co-oximetry results is required for a quantitative diagnosis. Treatment is based upon reduction of the oxidised methaemoglobin species back to haemoglobin. The limited case report literature supports methylene blue as a specific therapy, but other less validated therapies include ascorbic acid, renal filtration, and hyperbaric oxygen amongst others. In our case report, we describe the utility of ascorbic acid therapy when there may be concern for further oxidative injury from methylene blue, as in the setting of dapsone induced oxidative haemolysis.

Table 1. Oxygenation, measured and monitored values noted during days 1 and 2 of admission

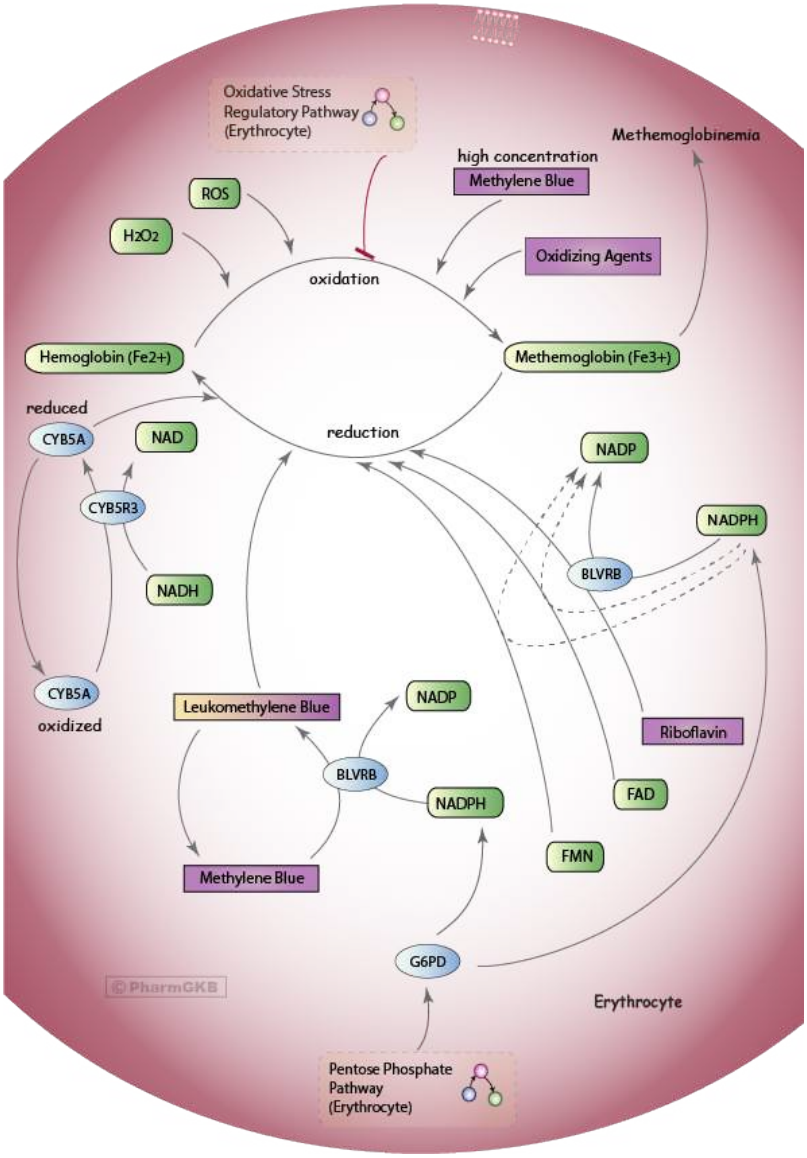
	Day 1				Day 2		Day 3	
FiO2	0.6	0.5	0.7	0.5	0.43	0.27	0.24	0.24
PaO2	80	192	258	128	168	117	106	94
SpO2	87	91	91	92	91	90	90	91
O2 Sat (ABG)	94	97	98	97	98	97	97	96
MetHb (%)	12	10.4	10.1	10.1	9.8	*	*	*

Legend: FiO2=fraction of inspired oxygen; PaO2=partial pressure of oxygen; SpO2=saturations measured by pulse oximetry; ABG=arterial blood gas; MetHb=methaemohaemoglobin; *=not done

Table 2. List of frequently encountered methaemoglobin precipitating drugs and compounds

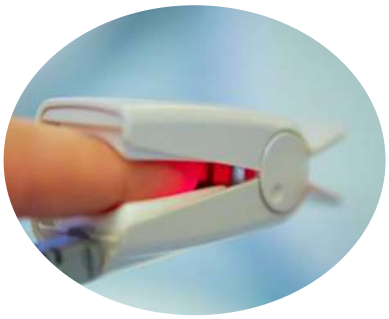
Local anaesthetics	Antimicrobials	Nitrates
Benzocaine	Chloroquine	Amyl nitrate
Prilocaine	Dapsone	Nitro-glycerine
Lidocaine	Sulfamethoxazole	Nitric oxide
	Rifampin	Nitroprusside
	Primaquine	
Antineoplastics	Dyes & industrial compounds	Antiemetics
Cyclophosphamide	Aniline	Metoclopramide
Ifosfamide	Aniline dyes	
Flutamide	Napthalene	
Sulphonamides	Anti-epileptics	Others
	Sodium valproate	Methylene blue
	Phenytoin	Rasburicase

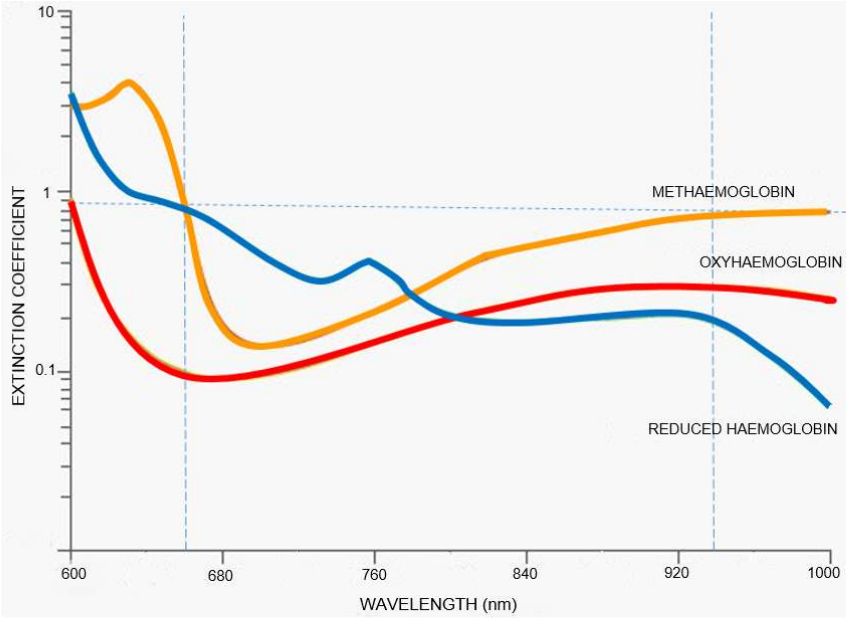
Figure 1. Stylized diagram showing the mechanisms that can cause methaemoglobin production in erythrocytes and the control mechanisms to prevent methaemoglobin, including methylene blue treatment, which requires NADPH from the pentose phosphate pathway



Legend: copyrighted image used with permission from PharmGKB and Stanford University (https://www.pharmgkb.org/pathway/PA165980834).

Figure 2. With pulse oximetry the absorbance of metHb at 660 and 940 is very similar and the ratio tends towards 1, which is computed and drives the saturation reading towards 85%





Legend: Drawn from data derived from Von Kampen EJ, 1983

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