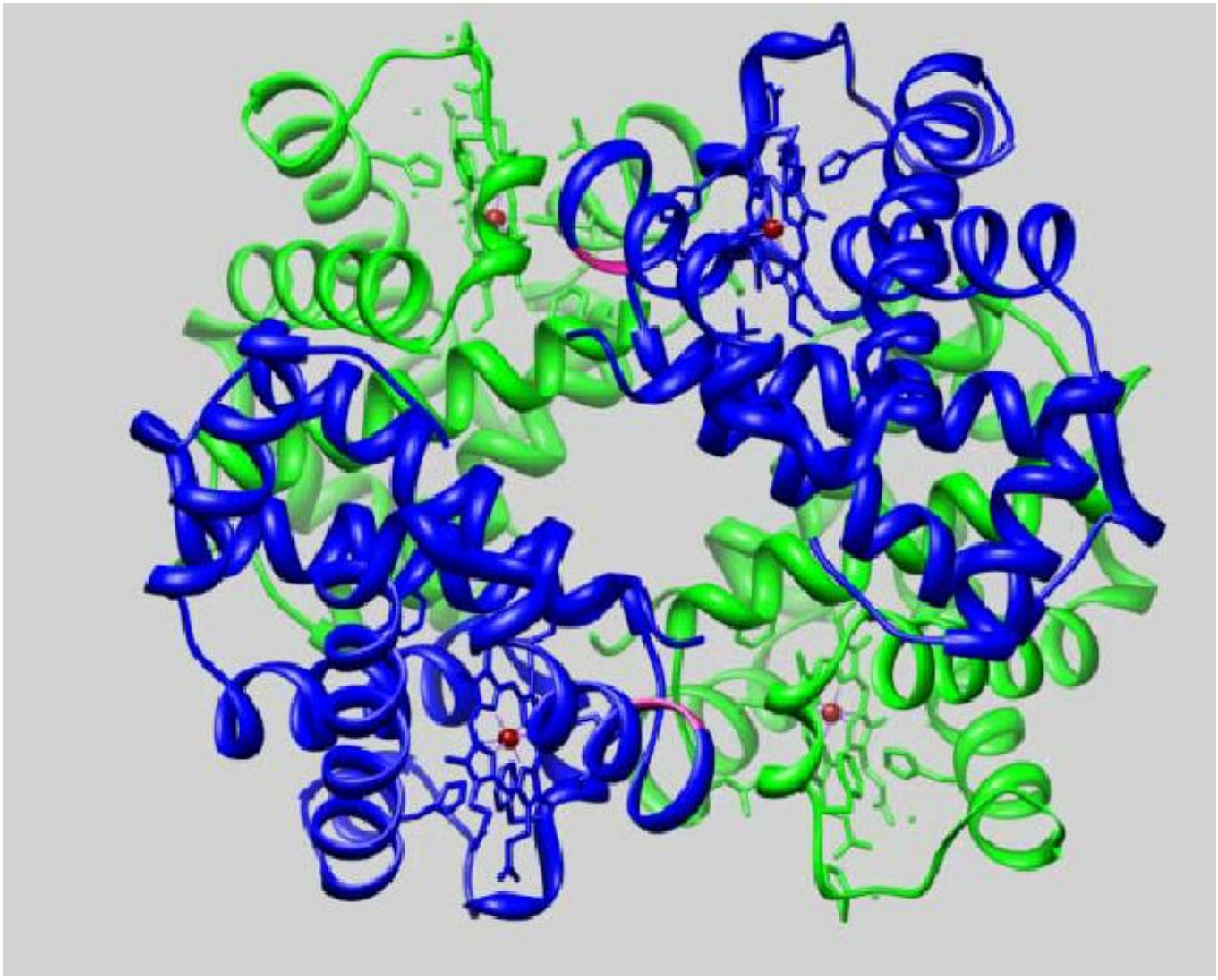
The Royal Melbourne Hospital

Perfusion Protocol – Methaemoglobinaemia



Haemoglobin contains iron within a porphyrin heme structure which is usually stable but auto-oxidises to methaemoglobin and superoxide. The iron in haemoglobin is usually found in the ferrous state however when oxidised to the ferric state, it becomes methaemoglobin. Methaemoglobin (MetHb) is therefore defined as the iron component of the haem moiety being in an oxidised or ferric state thus less able to 'give up' oxygen to the tissues. This can be a direct or indirect reaction depending on the agent involved. Levels in a 'normal' setting are around 1-2% in a healthy individual. Methaemoglobin is naturally occurring within us due to the auto-oxidation process but is physiologically reduced to ferrous haemoglobin by cytochrome B5 reductase maintaining levels around 1-2% within the body.

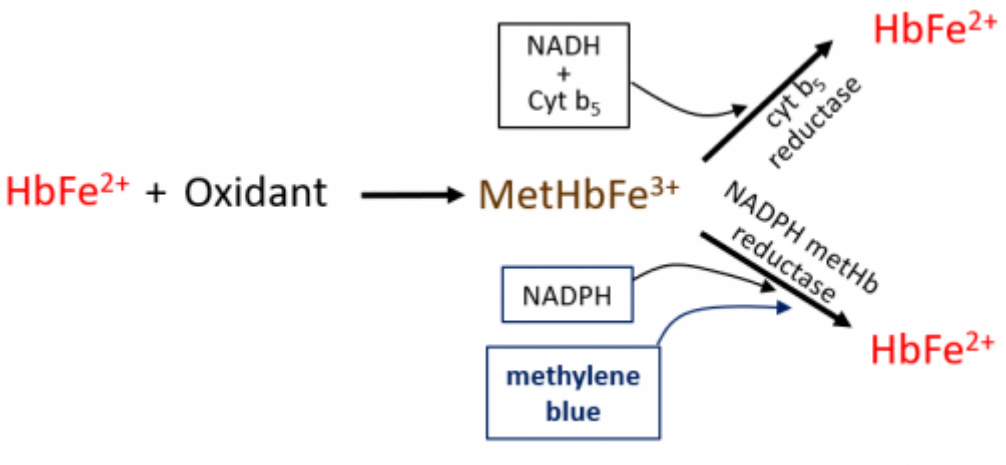


Figure 1: Methylene blue mechanism of action (*Curry, S.* Tox and Hound)

Symptoms/signs:

Methaemoglobinaemia is defined as high levels of methaemoglobin in the blood system (normal ranges being 1-2%). Levels around 20-30% (*Table 1*) can cause mental status changes, headache etc and levels in excess of 50% can result in dysrhythmias, seizures and in some cases death (Umbreit 2007). Drug exposure can cause an increase in oxidative stress therefore increasing methaemoglobin levels. An increase in MetHb can be accompanied by haemolysis and oxidative reactions occurring outside the vascular space can lead to cell damage in other organs including the liver or lungs (Wright 1999). Arterial blood is described as 'chocolate brown' and patients present with a 'blueish hue' (Chui 2005).

Methaemoglobin concentration	Clinical findings
1–3%	None
3–15%	Possibly none; pulse oximeter will read low oxygen saturations
15–20%	Cyanosis (central and peripheral); not improving with oxygen administration
20–50%	Dyspnoea, headache, fatigue, dizziness, syncope, weakness
50–70%	Tachypnoea, metabolic acidosis, dysrhythmias, seizures, central nervous system depression, coma
>70%	Grave hypoxic symptoms, death

Table 1(Hunter 2011)

Diagnosis:

According to several authors, methaemoglobin interferes with oximeter readings of oxygen saturation. This is due to the fact that methaemoglobin absorbs infrared light (940nm) and red light (660nm) equally therefore creating an absorption ratio of 1 (Chui 2005). Oxyhaemoglobin absorbs infrared light and deoxyhaemoglobin absorbs red light. Given that pulse oximetry measures only two wavelengths (oxyhaemoglobin and deoxyhaemoglobin) it cannot be used as a diagnostic tool. Co-oximetry can be used to determine methaemoglobin levels given that it measures 4 wavelengths: oxyhaemoglobin, deoxyhaemoglobin, carboxyhaemoglobin and methaemoglobin. ABG results will show the % of MetHb present and can be used to confirm a diagnosis. Communication with the poison's team would then be necessary.

Allosteric interactions increase the affinity for oxygen at remaining binding sites therefore shifting the oxygen dissociation curve to the left (*Figure 2*). When there are high levels of haemoglobin in this state it produces an anaemic hypoxia.

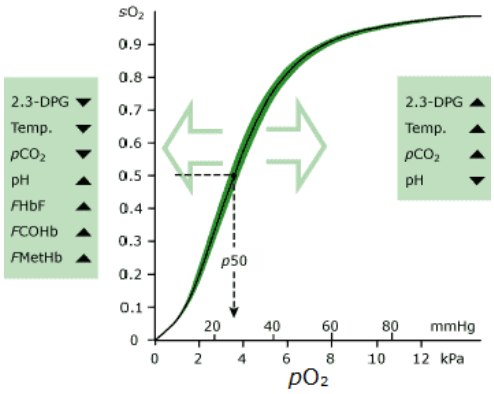


Figure 2: Dissociation curve

Causes:

Nitrites, Nitrates, drugs (e.g. dapsone)

Sodium nitrite is a yellowish/white powder and is used as a food additive, in dyes and also pesticides. It is also the antidote for cyanide poisoning. Accidental ingestion is often related to affected water wells and pipes (it is used as an anti-corrosive agent) it can also be intentionally ingested to cause harm and in the worst case scenario, death. The lethal oral dose reported for sodium nitrite is 0.7-6.0g. Nitrites are known to be potent vasodilators which can lead to coronary ischaemia and stroke due to hypotension. When ingested, there is an increase in oxidative stress when erythrocytes are exposed to nitrites: this is an indirect reaction which reduces the oxygen to the free radical and thus in turn leads to an increase in production of methaemoglobin.

Treatment:

Survival has been reported in cases where methaemoglobin levels were in excess of 70% (Chui 2005). It has been suggested that patients with a methaemoglobin <30% should only require minimal treatment but those with a higher MetHb level should be treated with methylene blue (administered at 1-2mg/kg over 3-5 minutes)(Chui 2005) and possibly red cell exchange. Methylene blue is a thiazine dye which acts as an electron donor and converts MetHb to haemoglobin. It achieves this by reduction to leucomethylene blue by NADPH-dependent methaemoglobin reductase and this in turn converts MetHb to haemoglobin (*Figure 1*). Methylene blue needs to be administered slowly in order to avoid a paradoxical MetHb production. Symptoms are reported to subside around 30-60 minutes after administration of methylene blue.

Snapshot of treatment:

- Confirm diagnosis on ABG (%MetHb)
- Talk with poison's team regarding treatment
- Methylene Blue administered at 1-2mg/kg over 3-5 minutes
- Consider red cell exchange on bypass

References

Bradberry, S.M. et al. Occupational Methaemoglobinaemia. *Occupational Environmental Medicine,* 2001; 58 (9): 611-616.

Chui, J.S.W. et al. Nitrite-induced methaemoglobinaemia – aetiology, diagnosis and treatment. *Anaesthesia*, 2005; 60: 496-500.

Curry, S. Continuous Methylene Blue Infusions for Treating Recurrent Methemoglobinemia. *Tox and Hound.*

ELSO – ECLS Registry Report: International Summary 2017.

Falkenhahn, M. et al. Unexplained acute severe methaemoglobinaemia in a young adult. *British Journal of Anaesthesia,* 2001; 86: 278-80.

Harvey, M. et al. Fatal methaemoglobinaemia induced by self-poisoning with sodium nitrite. *Emergency Medicine Australasia,* 2010; 22: 463-465.

Hunter, L. et al. Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: a review. *British Journal of Clinical Pharmocology,* 2011; 72:1:18-26.

Katabami, K. et al. Case Report: Severe Methemoglobinemia due to Sodium Nitrite Poisoning. *Case Reports in Emergency Medicine,* 2016; Article ID 9013816.

Umbreit, J. Methemoglobin – It's Not Just Blue: A Concise Review. *American Journal of Hematology,* 2007; 82: 134-144.

Wright, R.O. et al. Methemoglobinemia: Etiology, Pharmacology, Clinical Management. *Annals of Emergency Medicine,* 1999; 34:5: 646-656.