Methaemoglobinaemia

Introduction

Excessive methaemoglobin (MetHb) in the blood. In MetHb the ferrous ions (Fe^{2+}) of haem are oxidised to the ferric state (Fe^{3+}) and rendered unable to bind O_2. NADH & NADPH systems in the body normally keep the MetHb level<3%. $T_{\frac{1}{2}}$ = 1-3h if formation has stopped.

Causes

Congenital/Predisposition

- Cytochrome b5 reductase deficiency
- Diaphorase I deficiency (NADH methaemoglobin reductase deficiency)
- HbM disease
- HbH disease
- HbF (foetal Hb)
- G6PD deficiency (↓NADPH)
- Pyruvates kinase deficiency (↓NADH)

Acquired (toxin/drugs)

- Aniline dyes, herbicides (e.g. propanil)
- Benzene derivatives - naphthalene
- Chloroquine, primaquine
- Dapsone
- LA – prilocaine, benzocaine
- Metoclopramide
- Nitrates/nitrites (GTN, NO, SNiP)
- Well water (nitrates), nitrous gases
- Sulphonamides, trimethoprim
- Silver, chromates, Cu II salts
- Chlorates, bromates

Clinical Features

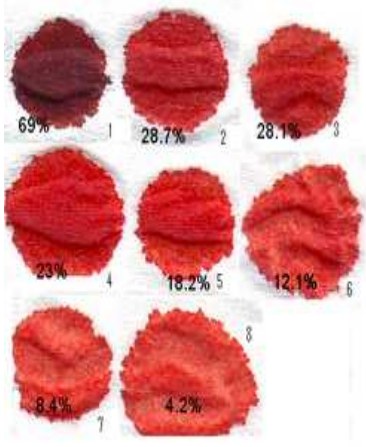
- Cyanosis unresponsive to O_2
- Symptoms & signs of hypoxaemia e.g. chest pain, SOB, ↓GCS, end organ damage
- SaO_2 reading 85-90% - MetHb absorbs light at similar wavelengths to oxy- & deoxyHb
- Blood samples typically have a chocolate brown hue

Investigations

- ABG – Pulse SaO_2 low but ABG shows normal PaO_2 & calculated Hb oxygen saturation

MetHb Level	Clinical Correlation
0-3%	Normal, physiological levels
10-20%	Chocolate brown blood & blue-grey skin not improved by O_2
20-50%	SOB, lethargy, headache, syncope, tachycardia
50-70%	Hypoxic behaviour, seizures, coma, arrhythmias, met acidosis
>70%	Death is likely if untreated

Management



Decontamination - remove or cease precipitant if possible

Resuscitation - High flow O_2 (to ensure available Hb is saturated)

Specific therapy

- Methylene blue (see below)
- Alternatives - used esp if methylene blue CI, e.g. G6PD def:
    - Exchange transfusion
    - Hyperbaric oxygen
    - Antioxidants: ascorbic acid (vit C), N-acetylcysteine, toluidine blue & tocopherol (vit E) unproven
    - Cimetidine if dapsone induced – reduces →MetHb, but doesn't ↓ existing MetHb
- Congenital - avoid precipitants

Supportive care and monitoring

Methylene Blue (Methylthioninium Chloride)

Provides artificial electron acceptor for MetHb reduction via the NADPH-dependent pathway.
Dose: 1-2mg/kg of 1% over 5 minutes followed by saline flush; repeat at 30-60 min if MetHb levels not falling repeat dose every 6-8h when MetHb continues for days, e.g. dapsone toxicity
Indications:

- Symptomatic
- Consider if asymptomatic with >20% metHb, or >10% if risk factors such as anaemia or ischemic heart disease
- (Has been used for antimalarial agent, anti-cancer Rx, ifosfamide neurotoxicity, priapism)

Reasons for failure of methylene blue:

- Massive ongoing exposure to an oxidising agent
- Sulphaemoglobinemia (e.g. dapsone, sulphonamides)
- G6PD deficiency
- MetHb reductase deficiency
- Abnormal haemoglobin
- Excessive methylene blue (paradoxical effect in high doses)

Mechanisms of action

- Low conc → leucomethylene blue (by methaemoglobin reductase) → reduces MetHb → Hb
    - But at high conc: Fe^{2+} of reduced Hb → oxidised to Fe^{3+} i.e. MetHb
- Inhibits guanylate cyclase, thus decreasing C-GMP and vascular smooth muscle relaxation
- MAO inhibition – risk of serotonin toxicity with other serotoninergic drugs

Contra-indications

- G6PD deficiency (↓NADPH prevents methylene blue working & may lead to haemolysis)
- Renal impairment (excreted predominantly by kidneys)
- Methaemoglobin reductase deficiency
- Nitrite-induced methaemoglobinaemia due to cyanide poisoning
- Hypersenstitivity

Adverse events

- Inability to monitor oxygen saturation by SaO_2
- Non-specific symptoms: dizziness, headache, confusion, chest pain, SOB, N&V
- Local pain and irritation
- Blue staining of mucous membrane may mimic cyanosis
- Paradoxical MetHb due to direct oxidative effect on Hb (typically doses > 7 mg/kg)
- Acute haemolytic anaemia in G6PD deficiency (typically doses >15mg/kg)
- Anaphylaxis
- MAO inhibition may contribute to serotonin toxicity or hypertensive crisis

Sulfhemoglobinemia

Sulfhemoglobin is a stable, green-pigmented molecule, not normally present in the body.
Sulfhemoglobinemia may mimic methaemoglobinaemia in several ways:

- Similar drugs (usually sulphur-containing, but when not sulphur is sourced endogenously)
- Cyanosis (needing only 0.5g/dL)

However, sulfhemoglobin is irreversible and SOB uncommon unless sulfhemoglobin level is high.
Sulfhemoglobin also shares an absorption peak with methemoglobin molecules at 630nm and so on older blood gas co-oximeters may be interpreted as MetHb.
Treatment for sulfhemoglobinemia is generally supportive only after removal of the offending agent. Exchange transfusion is rarely required.