ACQUIRED METHAEMOGLOBINAEMIA: What to do if methylene blue fails…

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METHAEMOGLOBINEMIA: DEFINITION

- Methaemoglobinemia = excess methaemoglobin (MetHb) in the blood
- In MetHb, haem iron is oxidized from $\text{Fe}^{2+} \rightarrow \text{Fe}^{3+}$
- $\text{Fe}^{3+}$ haemoglobin cannot bind oxygen
- Methaemoglobinemia $\rightarrow$ tissue hypoxia
- Methaemoglobinemia $\equiv$ oxidative stress
CASE 1
(after Dawson and Whyte, 1989)

- Previously fit 24 year-old man
- Dapsone overdose 16 x 50 mg
- C/O dizziness and headache
- [MetHb] 41%
- O/E blue but no respiratory distress
QUESTION
CASE 1: QUESTION 1

Dapsone-induced methaemoglobinaemia:

1. Will show normal oxygen saturations (>95%) on pulse oximetry
2. Is caused by a dapsone metabolite
3. Typically does not respond to methylene blue
4. Induces MetHb in the same way as amyl nitrite
CASE 1: QUESTION 1

Dapsone-induced methaemoglobinemia:

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2. Is caused by a dapsone metabolite
3. Typically does not respond to methylene blue
4. Induces MetHb in the same way as amyl nitrite
CASE 1

● Oxygen saturation by pulse oximetry was 86%

● Methylene blue 100 mg IVI over 15 minutes

● Symptoms resolved promptly

● 2 h after methylene blue [MetHb] 10%

● → ICU for observation
CASE 1

- Following day noted to be ‘cyanosed’ again
- C/O headache but otherwise well
- Recurrence of methaemoglobinemia with [MetHb] 34%
QUESTION
CASE 1: QUESTION 2

What is the most likely explanation for recurrence of methaemoglobinemia?

1. Glucose-6-phosphate dehydrogenase deficiency
2. A further dapsone OD
3. Persistence of dapsone metabolite
4. Intravascular haemolysis
CASE 1: QUESTION 2

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DAPSONE-INDUCED METHAEMOGLOBINAEMIA

Dapsone → Hydroxylamine
DAPSONE-INDUCED METHAEMOGLOBINEMIA
METHYLENE BLUE: MECHANISM

NADPH → MetHb Reductase → NADP⁺

Methylene blue (oxidised) → HbFe²⁺ → MetHbFe³⁺

Leucomethylene blue (reduced)
METHYLENE BLUE FAILURE: PROLONGED MetHb FORMATION

- MetHb caused by chemicals such as dapsone, aniline and propanil is due to a hydroxylated metabolite of the parent compound

- The metabolite enters a cycle of MetHb formation

- MetHb can persist for days
Management of Dapsone Poisoning Complicated by Methaemoglobinemia


Time after ingestion (days)

Concentration (%)

Methylene blue infusion (mg/h)

MB 100 mg
QUESTION
CASE 1: QUESTION 3

Which additional treatment would you recommend in this case?

1. Exchange transfusion
2. Multiple dose activated charcoal
3. Haemodialysis
4. Ascorbic acid 1 g IV qds
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METHYLENE BLUE FAILURE: G6PD DEFICIENCY

- G6PD is required for NADPH formation
- NADPH is an important reducing agent
- NADPH ↓ (or ↓↓ or ↓↓↓ ) in G6PD deficiency
METHYLENE BLUE FAILURE: G6PD DEFICIENCY
METHYLENE BLUE FAILURE: G6PD DEFICIENCY

[Diagram showing the reaction involving NADPH, MetHb Reductase, NADP⁺, Methylene blue (oxidised), Leucomethylene blue (reduced), HbFe²⁺, and MetHbFe³⁺]
CASE 2
(after Liao et al, 2002)

- 25 year-old man with G6PD deficiency
- Sprayed with aniline in occupational accident
- Presented 3 h later with nausea, dizziness and cyanosis
- [MetHb] 51%
QUESTION
CASE 2: QUESTION 1

Which of the following statements is correct?

1. There is a high risk of haemolysis
2. Intravenous ascorbic acid 10 g qds is the best treatment
3. Methylene blue administration will exacerbate methaemoglobinemia
4. Haemodialysis is the best treatment
CASE 2: QUESTION 1
Which of the following statements is correct?

1. There is a high risk of haemolysis
2. Intravenous ascorbic acid 10 g qds is the best treatment
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CASE 2

- The patient received IV methylene blue 0.5 mg/kg (total dose 40 mg)
- [Met Hb] ↓ 2.1%
- Discharged well the following day
- Represented 4 days later with jaundice, pallor and dizziness
CASE 2

- [MetHb] 9.5%
- Hb 7.4 g/dL
- Reticulocyte (immature red cell) count 9.3% (normal <2%)
- Heinz bodies (precipitated denatured Hb) on blood film
QUESTION
CASE 2: QUESTION 2

The most likely cause of the intravascular haemolysis / haemolytic anaemia is:

1. Methylene blue
2. Aniline
3. Neither 1. or 2.
4. Both 1. and 2.
CASE 2: QUESTION 2

The most likely cause of the intravascular haemolysis / haemolytic anaemia is:

1. Methylene blue

2. Aniline

3. Neither 1. or 2.

4. Both 1. and 2.
There is relative competition for NADPH between MetHb formation from aniline metabolite and Met Hb reduction by methylene blue.
Both processes were operational in this patient, at least initially.
METHYLENE BLUE FAILURE:
G6PD DEFICIENCY

Aniline/dapsone-derived free radicals
Maintenance of GSH to protect against haemolysis

NADPH

- Metabolite-induced MetHb production
- Antidotal action of methylene blue
CASE 2: QUESTION 3

What is the most appropriate treatment for haemolysis in this case?

1. Ascorbic acid IV 10 g qds
2. Red cell transfusion
3. Hyperbaric oxygen
4. Haemodialysis
CASE 2: QUESTION 3

What is the most appropriate treatment for haemolysis in this case?

1. Ascorbic acid IV 10 g qds

2. Red cell transfusion

3. Hyperbaric oxygen

4. Haemodialysis
METHYLENE BLUE FAILURE: EXCESS METHYLENE BLUE

- Excess methylene blue may precipitate haemolysis even in the absence of G6PD deficiency
- Methylene blue total dose
  - $< 5 \text{ mg/kg} \quad \text{very unlikely}$
  - $< 10 \text{ mg/kg} \quad \text{unusual}$
METHYLENE BLUE FAILURE: EXCESS METHYLENE BLUE

Methylene blue

- first suggested as MetHb *inducer* to treat cyanide poisoning
- doses < 10 mg/kg – unlikely to cause significant MetHb formation
- haemolysis inactivates NADPH
- haemolysis favours MetHb formation
ACQUIRED METHAEMOGLOBINAEMIA: What to do if methylene blue fails...

TRUE FAILURE? No response

APPARENT FAILURE? Transient response
ACQUIRED METHAEMOGLOBINAEMIA: What to do if methylene blue fails…

TRUE FAILURE
No response

Severe haemolysis
Severe G6PD deficiency

Exchange transfusion
(high dose IV Vit C)
ACQUIRED METHAEMOGLOBINAEMIA: What to do if methylene blue fails...

**APPARENT FAILURE**

- Transient response

**APPARENT FAILURE**

- Prolonged methaemoglobin production
  - Consider methylene blue infusion
  - Measures to enhance toxin elimination (HD/MDAC)

**Excess methylene blue**

- Haemolysis
  - Transfusion if severe

Toxins requiring metabolic activation: aniline, dapsone, propanil
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