University Hospitals Birmingham NHS
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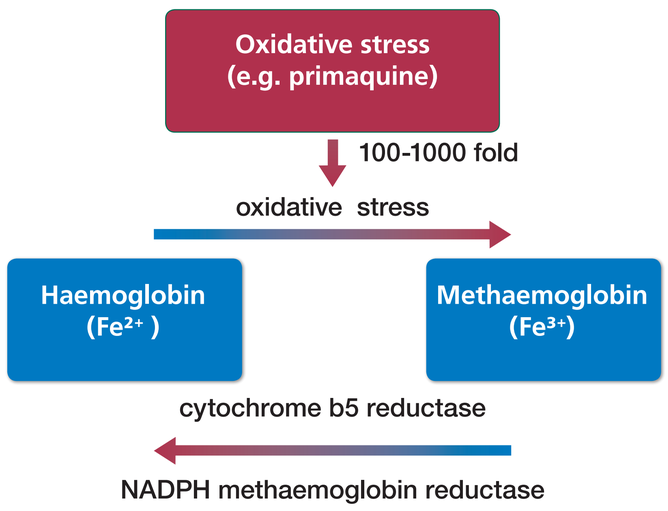
Primaquine induced Methaemoglobinaemia in a HIV positive patient on treatment for *Pneumocystis jiroveci* Pneumonia

Nyatsanza F, Manavi K
University Hospitals Birmingham, Birmingham, UK

Introduction

- Methaemoglobinaemia is a rare condition of unknown prevalence which is characterised by the presence of high levels of methaemoglobin. This is an oxidised form of haemoglobin which has a high affinity for oxygen. It leads to an overall reduced ability of erythrocytes to release oxygen and tissue hypoxia.
- By transferring electrons from NADH to methaemoglobin, which results in the reduction of methaemoglobin to haemoglobin1, cytochrome b5 reductase plays a major role in the control of methaemoglobin levels. This system is responsible for the removal of 95-99% of the methaemoglobin that is produced under normal circumstances.
- There are two types of methaemoglobinaemia – congenital and acquired. The congenital form is present at birth and can be caused by deficiency of NADH-cytochrome b5 reductase gene (b5R), pyruvate kinase, or abnormal forms of haemoglobin (HbM, or HbH).
- Exposure to exogenous oxidising drugs and their metabolites may accelerate the rate of methaemoglobin formation and by overwhelming the protective enzyme systems leads to acute increase in methaemoglobin levels and acquired methaemoglobinaemia (Figure 1).
- Methaemoglobinaemia has been reported with use of primaquine, dapsone and co-trimoxazole; antibiotics used for treatment and prevention of *Pneumocystis jiroveci pneumonia* (PCP).
- We describe a case of clinically significant primaquine induced methaemoglobinaemia in a newly diagnosed patient and discuss management and investigations for methaemoglobinaemia.

Figure 1. Methaemoglobinaemia mechanism



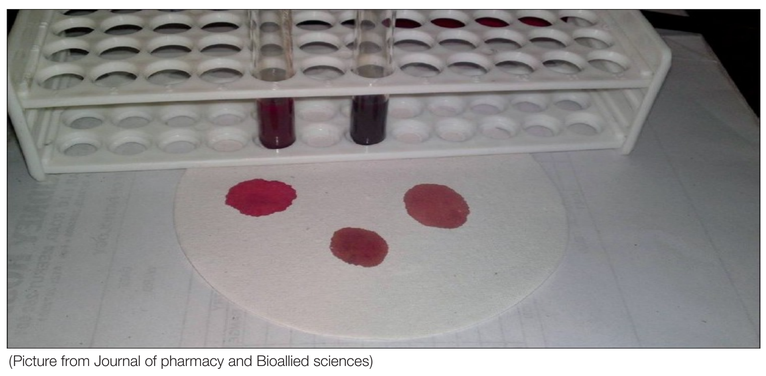
Case report

- A 38 year old was admitted with a three month history of weight loss, vomiting, nausea, night sweats and lethargy. He also had a productive cough and pyrexia for a week. He had a previous history of intravenous drug use and excessive alcohol intake.
- On examination, he was noted to have lymphadenopathy in the neck, and groin as well as, hepatosplenomegaly. He was admitted to hospital for community acquired pneumonia and possible lymphoproliferative disease.
- An HIV test was performed and patient was started on intravenous amoxicillin 1g three times a day.
- He was also started on co-trimoxazole 1920 mg three times a day for empiric PCP treatment. He was not Glucose 6 phosphate dehydrogenase (G6PD)deficient. A bronchoscopy with lignocaine spray was performed and computerised tomography of his chest, abdomen and pelvis showed non-specific bilateral cervical nodes, enlarged bilateral groin nodes and splenomegaly.
- Eight days after starting co-trimoxazole he developed a fever with a generalised macular rash. A septic screen was performed. An arterial blood gas, showed a pO2 of 11.23kPa and methaemoglobin levels within normal limits at 1.1% (0.4%-1.5%). Drug induced fever was considered a potential cause and co-trimoxazole was stopped. He was started on clindamycin 450mg QDS and primaquine 30 mg OD.
- A lymph node biopsy was performed nine days after start of primaquine and clindamycin. While in the recovery suite, patient developed dyspnoea with an oxygen saturation of 90% on pulse oximetry. An arterial blood gas was performed; pO2 was 22.23 kPa and methaemoglobin level 11.2%. Primaquine and clindamycin were stopped. As the patient was haemodynamically stable, methylene blue was deemed un-necessary. He was treated with supplementary oxygen. Four days later repeat methaemoglobin level was 6.2%.
- As bronchoalveaolar lavage for PCP PCR was negative, patient was commenced on monthly pentamidine 300 mg via nebuliser for PCP prophylaxis. Groin lymph node biopsy showed HIV related lymphadenopathy and no evidence of tuberculosis or lymphoma.
- At discharge he was given a list of medications to avoid as they may cause methaemoglobinaemia. The haematologists suggested measurement of cytochrome b5 reductase and glutathione reductase.

Discussion

- Methaemoglobinaemia is a recognised side effect with fatal consequences, especially when used in patients who have G6PD deficiency. It results from the enhanced production of methaemoglobin, a toxic ferric form of haemoglobin, by 8 amino-quinolones such as primaquine[3].
- Clinical presentation depends on the level of methaemoglobin in the blood. If methaemoglobin levels are less than 10%, then no symptoms are noted.
- At levels between 10-20%, cyanosis is noted on mucus membranes. If levels are between 20 -30 %, patients present with anxiety, headache, and dyspnoea on exertion. Typically, for levels between 30-50%, fatigue, confusion, dizziness, tachypnoea and palpitations are noted. Coma, seizures, arrhythmias and acidosis are noted at levels between 50% and 70%. Levels greater than 70% are usually fatal[3].
- Methaemoglobinaemia should be confirmed by arterial blood gas as pulse oximetry may give falsely reassuring oxygen saturation[4]. The best way of measuring methaemoglobin level is by carbon monoxide oximeter4.
- A simple bedside test is to place one or two drops of the patient's blood on white filter paper. The chocolate brown appearance of methaemoglobin does not change with time; whereas haemoglobin appears dark red/ violet initially but brightens after exposure to air (Figure 2)[4]. Other investigations include a potassium cyanide test where methaemoglobin reacts with cyanide to form bright red cyanomethemoglobin and measuring Cytochrome b5 reductase activity.
- If levels are below 30%, patients are treated by supplementary oxygen and withdrawing the causative agent. If there is no improvement, then methylene blue 1-2mg/kg can be used in patients with normal G6PD. For patients with G6PD deficiency, exchange transfusion or hyperbaric oxygenation can be used.
- There is documented evidence that discontinuing causative agents leads to clinical improvement as noted in our patient whose methaemoglobin level reduced from 11.2% to 6% in four days.

Figure 2. Normal blood colour compared with chocolate brown colour of blood in methaemoglobinaemia patient



(Picture from Journal of pharmacy and Bioallied sciences)

Conclusion

Methaemoglobinaemia should be considered in patients with cyanosis and oxygen saturation close to 90% who remain relatively asymptomatic. Prompt recognition and appropriate management of methaemoglobinaemia are essential in order to prevent fatality. It is important to consider iatrogenic causes of breathlessness (such as primaquine induced methaemoglobinaemia) when managing patients with *Pneumocystis jiroveci* pneumonia.

References

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