Vitamin C in Dapsone induced Methaemoglobinaemia- a case report

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Abstract

Dapsone had been used for leprosy but now used in dermatological conditions. The medical emergency team saw a patient on Dapsone with low oxygen saturation despite 8L/min O2 and elevated methaemoglobin level. After diagnosising dapsone related methaemoglobinaemia dapsone was ceased and Vitamin C given intravenously for 4 days

Dapsone induce Methaemoglobinaemia- a case report

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Key Clinical Message- Daspone therapy is associated with methaemogloinaemia. Pulse oximetry may indicate adequate oxygen saturations and co-oximetry is needed to diagnose low arterial oxygen saturations. Clinicans should be alert to this risk when prescribing dapsone

Case Report

A 23year old female initially presented to the hospital with a 1-week history of worsening blurry vision and mild headache which had progressed to ataxia and difficult ambulation. On examination she was found to have nystagmus, left eye ophthalmoplegia and diplopia with otherwise normal neurological examination and CT brain. She was admitted under neurology for further workup with a view to exclude Multiple Sclerosis (MS) amongst other differentials.

Her medical history was significant for Fibromyalgia and Mucha-Habermann Disease or Pityriasis lichenoides et varioliformis acuta (**PLEVA)** for which she has been on prednisone 30mg-50mg/day for 2 years and more recently Dapsone 150mg daily.

Three Days into her hospital admission , a Medical Emergency Team (MET) call was activated for ongoing hypoxia with pulse oximetry saturation (SpO2) ranging from 88-92% despite being on 8L of oxygen on the Hudson Mask. Upon arrival of the MET team, patient complained of dyspnoea and appeared tachypnoeic but denied cough, haemoptysis, chest pain or previous history of Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) or Acute Asthma attacks. On examination, her lips and fingertips appeared mildly blue; chest sounds were clear and heart sounds dual without any additional murmurs on auscultation and no lower limb tenderness or swelling were present. Her blood pressure was 103/66 mmHg and noted to be

in Sinus Tachycardia ranging from 90-105 beats per minute (bpm). A point of care (iStat) arterial blood gas analysis (ABG) was performed whilst patient was on 8L/min of oxygen with SpO2 90% which showed a PaO2 of 178 mmHg, SaO2 98%, PCO2 20mmHg, pH 7.56, bicarbonate 18 mmol/L, lactate 2.9mmol/L and Hb 98 g/L. On inspection of her medication chart, she had not received DVT prophylaxis for 3 days; so CT Pulmonary Angiogram (CTPA) was performed due to her high risk of thromboembolism. Both PE and Pneumonia were excluded on review. The patient was brought to Intensive Care Unit (ICU) due to ongoing hypoxia and placed on High Flow Nasal Prongs (HFNP). Her ABG in ICU (which includes co-oximetry analysis), showed a methaemoglobin (MetHb) level of 17.7% which then led to a diagnosis of dapsone induced methaemoglobinaemia. She was administered Vitamin C intravenously 10g every 6 hourly for 4 days prior to being switched to oral Vitamin C with MetHb returning to 1.3% after 5 days of treatment with SpO2 98-99% on room air oxygen.

Discussion

Dapsone Indications and Metabolism: Dapsone is a sulfone antibiotic and anti-inflammatory agent that inhibits folate synthesis(1). It has traditionally been used against leprosy but in the modern era, it has been prescribed for dermatological conditions including pyoderma gangrenosum, dermatitis herpitiformis and several infectious organisms like *Pneumocystis jerovici (PJP)* and toxoplasmosis (1-3). The metabolism of dapsone occurs through various P-450 enzymes in the liver to either N-acetyl dapsone or N-hydroxy dapsone and it is this latter metabolite which is thought to cause methaemoglobinaemia and haemolytic anaemia from oxidative stress (2, 4, 5). Dosages above 200mg/day is usually most frequently associated with methaemoglobinaemia(4).

Mechanism for Methaemoglobinaemia:

A single haemoglobin(Hb) molecule normally has four haem-iron complexes imbedded in the globin chains where the iron is in the Ferrous (Fe2+) state(6). When one oxygen reversibly binds to one haem-iron (Fe2+) complex, it makes it easier oxygen to attach to the remaining haem-iron (Fe2+) complexes due to the allosteric quaternary structure of haemoglobin(6). Methaemoglobin (MetHb) is an aberrant form of haemoglobin which occurs when the iron in the haem-iron complex changes from a ferrous (Fe2+) to a ferric (Fe3+) state by undergoing oxidation(2). The ferric state is unable to bind to oxygen and the oxygen affinity of any remaining haem-iron complex in the globin protein is increased which shifts the oxygen dissociation curve to the left (5, 7). Normally, auto-oxidation of Hb to MetHb occurs spontaneously which is paralleled by continuous reduction back to Hb via one dominant physiological pathway to maintain an equilibrium MetHb level of 1-2%(2, 5, 7); a second pathway does exist but remains mostly inactive unless an extrinsic electron carrier like methylene blue becomes available

Causes of Methaemoglobinaemia can be congenital or acquired with dapsone (including topical) being the most common but other offending agents include local anaesthetic benzocaine (especially spray 20%) and lignocaine (1, 2, 7, 8).

Clinical presentation and Diagnosis of methaemoglobinaemia: Clinically the symptoms depend on MetHb serum levels with peripheral and central cyanosis seen at 15% which was evident in our patient; headache, fatigue, tachycardia, weakness and dizziness at 30% to 45%; respiratory depression, paralysis, arrhythmia, convulsions and coma manifest at 60% and death at concentrations of 70% to 80% (1, 2, 4).

The ideal way to diagnose methaemoglobinaemia is to detect elevated serum levels of MetHb with a blood gas machine that has co-oximetry . But not all machines are equipped with co-oximeter so clinicians need to be aware of the phenomenon known as the “saturation gap” that arises in these cases (4). In our patient, even though her dyspnoea and tachypnoea had resolved, her saturation remained 88-90% despite being placed on to HFNP with FiO2 0.4 in the ICU which contrasted with her ABG analysis which showed a SaO2 of 98% with a PaO2 of 178mmHg. The reason behind this is twofold: the pulse oximeter measures SpO2 through absorption at two wavelengths (haemoglobin at 660nm and oxyhaemoglobin 940nm) which drops as MetHb

starts to rise and plateaus at around 85%(4, 5); the ABG machine measures arterial oxygen partial pressure which remains normal in methaemoglobinaemia and estimates oxygen saturation by using the standard oxyhaemoglobin dissociation curve (ODC)(7). Due to these factors, a so called "saturation gap" arises that should alert clinicians to the presence of an alternate non-functional Hb species. Our ICU ABG machine showed the oxyhaemoglobin level to be at 81%, demonstrating that the pulse oximeter overestimates the SpO2 in these scenarios and cannot be a reliable marker of arterial oxygen saturation(1, 4, 5, 9). Clinically the blood from this condition is described as "chocolate brown"(1, 7)

Management of methaemoglobinaemia: In most cases methylene blue (MB) is the first choice of treatment but high dose Vitamin C (VC) provides an alternative and effective management strategy (7, 11). Vitamin C was chosen in our patient because she had an unknown glucose-6-phosphate dehydrogenase (G6PD) status and had become reasonably stable without any further respiratory distress (most likely caused by anxiety). Vitamin C 10g every 6 hours was administered which led to the decline of MetHb to 1.3% in four days(Figure 1). Park and colleagues also used this regime for a patient that had MetHb level of 64.4%continued until MetHb fell below 10% at 54 hours post presentation. Further MetHb measurements showed ongoing decline despite cessation of VC therapy(11). The mechanism of VC therapy is not well understood but postulated that it removes oxidative stress, the main causative factor for methaemoglobinaemia(11). High dose VC also avoids rebound methaemoglobinaemia seen when repeated doses of MB are needed and hypoxia from haemolysis in those deficient of G6PD (1, 2, 7). Vitamin C can increase the urinary excretion of oxalate which in the context of renal disease can lead to renal failure due to hyperoxaluria (11)

Methylene blue is the 1st choice of treatment especially in the acutely unwell patient where a standard dose of 1-2mg/kg over 5 minutes can lead to a rapid decline in MetHb levels with a second dose rarely being needed (7). Moulis and colleagues showed that in their patient MetHb level of 17% fell to 4% in 20minutes after a 2mg/kg dose of MB but ten days later the patient had rebound methaemoglobinaemia at 14% which was attributed to the long half-life of dapsone; MetHb eventually declined to 5% the next day without any intervention (12). Methylene blue works by utilising the normally dormant G6PD pathway to act as an electron transporter to ultimately reduce MetHb back to Hb (Figure 2)(4, 7).

Conclusion: Methaemoglobinaemia is a rare cause for hypoxia and tachypnoea. Methaemoglobin levels can be elevated in patients on dapsone and should be considered as cause for hypoxia and tachypnoea in patients on dapsone. Methaemoglobin levels are available on most modern blood gas analysers to aid diagnosis . Vitamin C or methylene blue are recommended treatments for methaemoglobinaemia.

Author contribution

Dr Hasanul Kabir,- writing manuscript and literature review

Dr Ramnathan Lakshmanan,- writing manuscript and literature review

Dr Sumana Gopinath, writing manuscript and literature review

Assoc Prof Deepak Bhonagiri- corresponding author, writing manuscript and literature review

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FIGURE LEGENDS

Figure 1: Changes in plasma methaemoglobin concentration from time of diagnosis. Vitamin C therapy was started soon after and ceased prior to discharge after normalisation of methaemoglobin levels.

Figure 2: The physiologically dominant pathway for methaemoglobin reduction is through cytochrome P-450 shown in bold. Methylene Blue provides an alternate pathway through NADPH-G6PD

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