Methemoglobinemia – The Cryptic Cause of Dyspnoea

Kavita Krishna[1], Baldeep Singh[2], Vivek Nikam[2], Rohit Jakhotia[2], Vrushabh Phade[2]

Abstract

Methemoglobinemia is a life threatening condition that can be difficult to diagnose. It can be congenital or, more often an adverse drug effect. A good, detailed history taking and thorough knowledge of drugs and toxins is the secret to early diagnosis. We present two interesting cases of methemoglobinemia. First was phenol poisoning with G6PD deficiency leading to hemolysis and methemoglobinemia and second was phenol induced methemoglobinemia. Here we discuss the diagnosis and management of a patient with acquired methemoglobinemia.

Introduction

The majority of cases of acquired methemoglobinemia described in literature have resulted from exposure to exogenous oxidizing agents like nitrites used as preservatives in food or as a deliberate poison[1] amyl nitrate used as a recreational agent, abuse of paint thinner by addicts, intake of nitrate containing vegetables use of EMLA cream and Dapsone intake.

Phenols like dinitrophenol and pentachlorophenol are very toxic substances. They have significant inhibitory effect on various enzymes; such as G6PD. G6PD deficiency can lead to hemolytic crisis, favism, and chronic nonspherocytic hemolytic anemia.

Dapsone (4,4'- diaminodiphenyl sulfone) is a sulfone antibiotic and potent anti- inflammatory that inhibits folate synthesis.[2] It is metabolised in liver via the cytochrome P450 pathway to potent oxidants that are responsible for its adverse hematological effects – hemolytic anemia and methemoglobinemia.

Here, we report 2 cases of methemoglobinemia following ingestion of phenol and dapsone respectively.

Case Report 1

A 28 year old male, computer engineer by profession, admitted with alleged history of consumption of 300 ml phenol 6 hrs back, with complaints of oral and posterior pharyngeal wall ulceration, odynophagia, mild dyspnoea and abdominal pain.

His blood pressure was 120/80 mm of Hg with SpO2- 85%. On investigating, his laboratory parameters revealed: Haemoglobin – 13.0 g/dl; WBC – 15600 /cumm; Platelet count 2.20 lakhs/cumm, Serum bilirubin (T)-1.4, (I)- 1.0 mg/dl, Arterial blood gas showed pH-7.4, PO2- 92 mmHg, SpO2- 90%, rest WNL and Chest Xray and ECG were normal.

Patient started passing dark brown urine for which we repeated laboratory parameters after 6 hrs, which were suggestive of haemolytic picture s/o Hb - 11.5g/dl (↓), bilirubin (T)- 6.75 mg/dl (↑), (I)- 6.58 mg/dl (↑), Serum LDH- 1024 U/L (↑), G6PD levels were- 2.75 (4.6-13.6) U/ gm of hemoglobin, Methhemoglobin-14.54 (0-1.5%) of total Hb, Renal functions WNL, Urine routine- albumin- 3+, RBC-8-10/hpf

Plenty of oral and IV fluids were given. Urine output, haemogram and liver function tests were monitored. Because of G6PD deficiency methylene blue was not given. Patient was given Ascorbic acid 1 gram daily for 2 weeks. Over next 1 week his liver functions improved and he was discharged.

Case Report 2

48 yrs male known case of leukocytoclastic vasculitis (diagnosed on biopsy in 2012), with palpable purpura over the legs had been on varied immunosuppressive medications (Dapsone, Azoran and Mycophenolate mofetil) and steroids, to which he responded well. Patient was on irregular treatment and had omitted all medications since 6 months except for steroids (Tablet Methylprednisolone 2mg OD).

This time, he had complaints of increased rash over the legs since 2 weeks, for which he was started on tablet Dapsone 100 mg BD 7 days before. There was no history of fever, joint pain, hematuria. On admission, patient also had complaints of shortness of breath and tingling sensation over the head since 5 days.

Blood pressure was 120/80 mm of Hg, Pulse was 86/min, SpO2- 85 %. On investigating, his investigations were as follows:

Chest X-ray was normal, HRCT chest was suggestive of early interstitial lung disease and PFT's showed mild restrictive disease.

Pulmonologist advised to increase methyl prednisolone to 8mg, to continue dapsone, and added formoterol + budesonide inhalation. Later on taking detailed history, patient gave history of shortness of breath and similar symptoms 2 years ago after starting dapsone.

ABG s/o pO2- 88 mmHg, pCO2- 38, SpO2 – 90%

Blood was reddish brown colour, Methhemoglobin levels were 5.2% and G6PD level were normal.

Patient was advised to stop Dapsone. Since methhemoglobin levels were not very high, he was given iv ascorbic acid and Methylene blue was not given. Over the next 5 days patient's dyspnoea improved, Spo2 was 96-97% off o2 and was discharged on day 5.

Meth Hb after 15 days was 2% and normal after 2 months. On follow up, patient was asymptomatic on 4 mg methyl prednisolone, with no other symptoms and counselled to start Azoran/mycophenolate mofetil.

Discussion

In the first case, patient presented with haemolytic anaemia with mild hepatic injury, due to toxic injury with

[1]Professor, [2]Resident, Dept. of Medicine, Bharati Vidyapeeth Deemed University Medical College, Pune, Maharashtra, India
Received: 16.02.2017; Accepted: 06.03.2018

phenol was postulated. Acute toxicity causes intense burning sensation in mouth, throat, and stomach. Phenol is rapidly absorbed in the blood and there may be hyper or hypothermia, tachycardia, tachypnoea, generalised weakness, dizziness, nausea and shock leading to death. The average fatal dose is 2 gram and the half life as per pharmacokinetic studies in monkeys in 72-83 hours. It is excreted chiefly in the urine and also by the liver, lungs and skin.[3] Derivatives of phenol like dinitrophenol, pentachlorophenol interfere with oxidative phosphorylation in cells. Storage of energy in the form of adenosine triphosphate is prevented, thereby leading to a compensatory increase in the basal metabolic rate which is responsible for most of the principle clinical features of toxicity of this substance.

The main source of energy in red blood cells is anaerobic glycolysis. Due to shortage of energy, red blood cells cannot continue to perform their vital functions like preventing the osmotic equilibrium across the cell membranes, the cation pump and cell deform ability. This metabolic handicap may lead to premature lysis of the cells causing hemolysis. Also phenol may produce Heinz bodies and contribute to hemolysis.[4]

The mechanism that protects the red cells against oxidants include G6PD, the entry enzyme to the hexose monophosphate shunt that generates NADPH and the related enzymes that maintain GSH in the reduced form and protect haemoglobin from irreversible oxidation. Heinz body anaemias are found in individuals with defects in these protective mechanism when they are exposed to oxidants in the form of chemicals or drug that normally are not haemolytic. Low G6PD level explains the moderate haemolysis that develops after phenol poisoning as in our patient. Anaemia will be first noted as asymptomatic drop in spO2 and the appearance of bluish discolouration is an immediate clue to the presence of methemoglobinemia which is produced from oxidation of ferrous to ferric ions which cannot carry oxygen.

In second case, after detailed history, methemoglobemia secondary to dapsone was suspected and methemoglobin levels were sent. Dapsone is a drug that is used in the treatment of leprosy, dermatologic conditions like acne vulgaris, pyoderma gangrenosum and dermatitis herpetiformis, and various rheumatological disorders like systemic lupus erythematosus, Giant cell arteritis, vasculitis, relapsing polychondritis etc owing to its immunosuppressive effects. Long-term administration of dapsone at standard doses (100 mg/day) results in methemoglobinemia in about 15% of patients.[5] The peak plasma concentrations of Dapsone are reached within 2-8 hours after ingestion. The mean elimination half-life varies from 10 up to 80 hours in overdose situations. In healthy erythrocytes, cellular enzymes rapidly reduce any naturally occurring methHb. An exposure to oxidative medications can overcome these reducing enzymes thus causing an accumulation of methaemoglobin.[6] The role of nitric oxide (NO) in the pathophysiology of methemoglobinemia is also being studied.[7] Our patient became symptomatic within 1 week of starting Dapsone. Methemoglobinemia after short duration of therapy is uncommon.

ABG is the appropriate diagnostic test and brown colour of arterial blood is another useful clue to the presence of methemoglobinemia but co-oximetry is the gold standard. Methylene blue and ascorbic acid is given to reduce the methemoglobinemia. IV methylene blue ordinarily used in the treatment of severe (>20% methemoglobinemia) or symptomatic methemoglobinemia is ineffective in G6PD deficient patients since methylene blue works through the alternate pathway (NADPH dependent). Furthermore, methylene blue will exacerbate NADPH deficiency in such patients resulting in increased free radicals and a hemolytic crisis.[8] In such cases, ascorbic acid, a potent antioxidant and reducing agent is used.[9]

Conclusion

- Diagnosis of methemoglobinemia requires a high index of suspicion. A good, detailed history taking and thorough knowledge of drugs and toxins is the secret to early diagnosis.
- In patients with G6PD deficiency, phenol can cause methemoglobinemia and significant hemolysis.
- Methemoglobinemia should be considered of possibility if a patient on Dapsone complain of shortness of breath.
- Methylene blue should not be administered in asymptomatic cases and until after G6PD levels are shown to normal and ascorbic acid should be given instead.

References

1. Nabukeera-Barungi N, Mworozi E. Sudden onset methaemoglobinaemia in a previously well Ugandan child: A case report and literature review. *Pan Afr Med J* 2012; 11:49.
2. Zosel A, Rychter K, Leikin JB. Dapsone-induced methemoglobinemia: case report and literature review. *Am J Ther* 2007; 14:585–7.
3. Subramanyam BV (ed): Modi's Medical Jurisprudence and Toxicology. Butterwroths India, New Delhi, 22nd Edition 1999; (section 2): 55.
4. Hassan AB, Seligmann H, Bassan HM. Intravascular hemolysis induced by hexachlorophenol. *Br Med J* 1985; 291:21-2.
5. Coleman MD, Rhodes LE, Scott AK, Verbov JL, Friedmann PS, Breckenridge AM, et al. The use of cimetidine to reduce dapsone-dependent methaemoglobinaemia in dermatitis herpetiformis patients. *Br J Clin Pharmacol* 1992; 34:244–9.
6. Steiner IP, Nichols DN. A case of dapsone-induced cyanosis in the emergency department. *Isr J Emerg Med* 2006; 6:10–3.
7. Sanyal T, Chakraborty S. Multiscale analysis of hypoxemia in methemoglobin anemia. *Math Biosci* 2013; 241:167–80.
8. Rosen PJ, Johnson C, McGehee WG, et al. Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. *Ann Intern Med* 1971; 75:83–86.
9. Dunne J, Caron A, Menu P, et al. Ascorbate removes key precursors to oxidative damage by cell-free haemoglobin in vitro and in vivo. *Biochem J* 2006; 399:513–524.