INTRODUCTION

Dermatologists commonly employ dapsone in the dosing range of 50–200 mg/day (2 mg/kg) in the management of leprosy, neutrophilic, autoimmune bullous, and granulomatous disorders. Among hematologic adverse effects of dapsone, Heinz body anemia and methemoglobinemia are peculiar adverse reactions which need prompt diagnosis and treatment. Methemoglobinemia is a potentially life-threatening disorder that requires immediate medical attention. In this short review, authors will discuss the pathophysiology, diagnosis, and management of dapsone-induced methemoglobinemia.

PATHOPHYSIOLOGY OF METHEMOGLOBINEMIA

Methemoglobin (MetHb) or ferrihemoglobin is the oxidized form of hemoglobin (Hb), which does not bind oxygen and increases the affinity of oxygen for the partially oxidized portion of Hb. MetHb develops when heme iron is in the ferric state (Fe$^{3+}$) instead of the normal ferrous state (Fe$^{2+}$). Oxidized iron (Fe$^{3+}$) in the heme moiety leads to the left shift of the oxygen dissociation curve and reduced oxygen delivery at the tissue level as remaining normal monomers of ferrous heme within a Hb tetramer bind their oxygen more tightly. Under normal circumstances, erythrocytes constantly produce low levels of MetHb (1%) secondary to various oxidative stresses. Fortunately, MetHb levels are kept under check through the regulatory actions of three enzyme systems working synchronously: (i) Nicotinamide adenine dinucleotide (NADH)-methemoglobin reductase (NADH-MR), a system with two enzymes, cytochrome B5 and cytochrome B5-reductase (CB5R), is responsible for the endogenous reduction of MetHb, corresponding to 99% of the reducing activity. (ii) nicotinamide adenine dinucleotide phosphate (NADPH)-dependent MetHb reductase (~5% of the conversion), and (iii) nonenzymatic antioxidants ascorbic acid and glutathione (~12–15% of the conversion).[1] Additional minor pathways of MetHb reduction include those involving tetrahydropterin, cysteamine, reduced flavin, and reduced cysteine on protein molecules.[2]

HOW DAPSONE CAUSES METHEMOGLOBINEMIA

Dapsone is one of the commonly used drugs known to cause methemoglobinemia. Both hydroxylamine derivates of dapsone are equipotent in their MetHb forming ability. Inside the erythrocytes, hydroxylamine derivates deliver a severe oxidative stress to Hb in the red blood cells superseding the compensatory physiologic reductive capacity. Oxidative damage converts Fe$^{2+}$ in the heme to Fe$^{3+}$ and thus reduces the affinity for oxygen thereby making Hb an inadequate oxygen transporter. A single ferric (Fe$^{3+}$) ion in the Hb tetramer makes remaining ferrous ion (Fe$^{2+}$) to bind oxygen more tightly and causes a left shift of the Hb-oxygen dissociation curve which implies poor oxygen delivery at tissue level and resultant hypoxia at cellular level.[3]

CLINICAL FEATURES OF METHEMOGLOBINEMIA

Clinical signs and symptoms entirely depend on the percentage of oxidized Hb (MetHb). Mild methemoglobinemia (2%–10% of total Hb) is well tolerated and is usually asymptomatic in an apparently healthy individual. MetHb levels above 10%–15% cause bluish to slate-gray discoloration of the skin, an earliest sign of tissue hypoxia. Symptoms of severe tissue hypoxia.

HOW TO MANAGE A SIDE EFFECT: DAPSONE-INDUCED METHEMOGLOBINEMIA

How to manage a side effect: Dapsone-induced methemoglobinemia. Indian J Drugs Dermatol 2016;2:117-20.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.
hypoxia result from MetHb above 20% and include tachycardia, headache, dizziness, and anxiety while levels above 50% cause severe respiratory distress and fatigue and lastly toxic levels above 70% frequently prove to be fatal. A peculiar chocolate-brown color blood rather than the dark red of deoxygenated venous blood or bright red oxygenated arterial blood suggests MetHb above 20%.

Table 1 summarizes the clinical signs and symptoms of methemoglobinemia.

Paradoxically, even low levels of MetHb can cause severe signs and symptoms in patients who have preexisting conditions that compromise peripheral oxygenation of tissues (e.g., anemia, respiratory, or cardiac diseases). Dapsone-induced methemoglobinemia may get worsened if there exists concomitant hemolysis.

**DIAGNOSIS**

In an appropriate clinical setting, a high index of suspicion is necessary for making a diagnosis of iatrogenic or acquired methemoglobinemia. Basic laboratory tests include complete blood count (low Hb), reticulocyte count (increases due to hemolysis if any), and G-6PD estimation. However, exact diagnosis depends on few other tests. Pattern recognition is a key to diagnose methemoglobinemia (cyanosis, low Hb saturation on pulse oximetry [SpO2]), and normal partial pressure of oxygen [pO2] on arterial blood gas analysis and chocolate blood on sampling.

pO2 in the blood is the function of small amount of oxygen dissolved in the plasma and not bound to Hb. MetHb does not impair delivery of oxygen to blood plasma in the alveoli and thus pO2 remains unaffected. Oxygen saturation (sO2) reflects the oxygen bound to Hb in red blood cells, and since MetHb has poor affinity for oxygen, methemoglobinemia is associated with reduced sO2. Arterial oxy-Hb saturation measured by an arterial blood gas analysis is called SaO2 while arterial oxy-Hb measured noninvasively by a finger pulse oximeter or handheld pulse oximeter is called SpO2. An important caveat should be borne in mind that sO2 estimation in methemoglobinemia obtained on blood gas analysis can be misleading since the calculations are based on the assumption of normal oxygen dissociation curve and absence of other altered Hb.

Similarly, SpO2 readings from pulse oximeter, a noninvasive spectrophotometric method, can be misleading in patients with MetHb since the method employs red and infrared light absorption characteristics of oxygenated and deoxygenated Hb at 660 nm (red light) and 940 nm (infrared light), respectively, and assumes the absence of abnormal Hbs.

The use of only two wavelengths limits the discriminatory capacity of the oximeter to only oxy- and deoxy-Hb. Pulse oximeters usually assume that there are no nonfunctioning Hbs in the arterial blood.

A “saturation gap” between the recorded saturation from the pulse oximeter as compared to the reported saturation in the arterial blood gas may be detected and in the presence of a high index of suspicion, may be the key to diagnosis, especially in the resource-limited setting.

To counteract the above shortcomings, a new technological advance named multiple wavelength CO-oximetry has been incorporated in the blood gas analysis systems and is being considered as gold standard for diagnosis of methemoglobinemia. A CO-oximeter is a device that measures the oxygen-carrying state of all Hb derivatives in a blood specimen including oxygen-carrying Hb, nonoxygen-carrying but normal Hb as well as the dyshemoglobins such as carboxyhemoglobin and MetHb. A useful practical tip is to use CO-oximetry before administering methylene blue. Once methylene blue has been injected, CO-oximetry cannot be repeated as methylene blue is read as MetHb by the machine since both shares similar absorbance characteristics.

Recently, few workers from Sri Lanka have developed simple bedside tool for semiquantitative estimation of MetHb levels and can be used in resource-poor settings.

**TREATMENT**

Methylene blue (methylthioninium chloride trihydrate) is the antidote of choice for reversing methemoglobinemia and should be reserved in cases where MetHb is more than 30%. Methylene blue is a compound consisting of dark green crystals or crystalline powder, having a bronze-like luster. Solutions in water or alcohol have a deep blue color. Methylene blue is used as a bacteriologic stain and as an indicator. It inhibits guanylate cyclase and has been used
to treat cyanide poisoning. Methylene blue is an oxidizing agent while its metabolite leukomethylene blue is a reducing agent. Methylene blue 10 mg/ml (1%) solution is to be used in the dose of 1–2 mg/kg body weight intravenously every 5 min. The dose can be repeated after 30 min if cyanosis does not improve. Since the source of NADPH is aerobic glycolysis in the red blood cells, methylene blue treatment should be accompanied with intravenous (IV) dextrose infusion. Within red blood cells, methylene blue activates NADPH-MR to form leukomethylene blue, which acts as a reducing agent (electron donor) of oxidized Hb, converting the ferric ion (Fe³⁺) back to its oxygen-carrying ferrous (Fe²⁺) state. The above mechanism needs normal levels of G-6PD activity and adequate production of NADPH to reduce methylene blue to leukomethylene blue, and lack of response to methylene blue should incite the physician for estimation of G-6PD levels. The maximum approved dose of methylene blue is 7 mg/kg. Higher doses of methylene blue exceeding 7 mg/kg may paradoxically worsen methemoglobinemia owing to its oxidizing potential at higher dose range. The use of methylene blue is not recommended in infants under 4 months of age. In spite of methylene blue treatment, one must bear in mind that rebound methemoglobinemia can occur since half-life of hydroxylamine metabolite is around 30 h and may persist in the systemic circulation for about 35 days. Hence, one must forewarn the patient about this possible rebound phenomenon and to report back if any cyanosis recurs.

**METHYLENE BLUE AND G-6PD DEFICIENCY**

Inside the red blood cell, methylene blue acts by forming leukomethylene blue; this is a reducing agent of oxidized Hb converting the ferric ion (Fe³⁺) back to its oxygen carrying ferrous state (Fe²⁺). G-6PD plays a key role in methylene blue-mediated reversal of methemoglobinemia as G-6PD-deficient individual does not generate sufficient NADPH to efficiently reduce methylene blue to leukomethylene blue catalyzed by biliverdin reductase B, which is necessary for the activation of the NADPH-dependent MR system. Thus, administration of methylene blue is counterproductive in G-6PD deficient individuals having methemoglobinemia and can paradoxically serve as an oxidant stress and can cause hemolysis. Hence, it is a clinical dictum before using methylene blue in the treatment of MetHb - “Blue cures blue but be cautious.” The logical conclusion that follows from discussion is that administration of methylene blue is contraindicated in patients having G-6PD deficiency. The physician should remember that G-6PD deficiency is a risk factor for dapsone-induced hemolytic anemia but not for methemoglobinemia unless concurrent oxidizing drugs are given.

Adverse effects associated with administration of methylene blue include anemia, nausea, vomiting, diarrhea, a burning sensation in the mouth or dyspnea, restlessness, and sweating. Higher dosage in the range of 15 mg/kg causes direct damage to red blood cell with resultant hemolysis and Heinz body formation. The primary route of excretion of methylene blue is renal, predominantly as leukomethylene blue and should be used cautiously in mild to moderate renal impairment. Coadministration of methylene blue and serotonergic agents is not recommended due to risk of serotonin syndrome. Methylene blue blocks the breakdown of serotonin in the brain by inhibition of enzyme monoamine oxidase A. If coadministration of methylene blue and serotonergic drugs is warranted then physician must be aware of central nervous system signs and symptoms (i) neuromuscular hyperactivity: tremor, clonus, myoclonus and hyperreflexia, and, in the advanced stage, pyramidal rigidity; (ii) autonomic hyperactivity: diaphoresis, fever, tachycardia, tachypnea, and mydriasis; and (iii) altered mental status: agitation and excitement, with confusion in the advanced stage.

Prophylactically, cimetidine can be given to reduce hepatic oxidation of dapsone to the hydroxylamine through inhibition of cytochrome P-450 enzyme system. Cimetidine does not appear to treat preexisting levels of MetHb in the blood. Concurrent administration of cimetidine allows the use of higher dose of dapsone >200 mg/day and keeps the level of MetHb below 30%. In G-6PD deficient patients where methylene blue is contraindicated and unavailability issues, Vitamin C can be considered for reversing methemoglobinemia. In various studies and case reports, different dosing regimens were used to treat methemoglobinemia (300 mg/kg IV bolus, 300 mg IV in 24 h, and 10 g IV in 6 h) and thus imply that there is no consensus regarding dose and duration.

Exchange transfusion can be considered in cases where methylene blue therapy is ineffective. The principle involves removal of MetHb-containing red blood cells from the affected patient through the removal of aliquots of blood and replacing it with donor cells.

N-acetylcysteine, cimetidine, and ketoconazole are experimental therapies in the treatment of methemoglobinemia that have shown some promising results.
CONCLUSION

Methemoglobinemia is a potentially life-threatening condition which requires a high index of suspicion, appropriate laboratory workup, and intelligent interpretation and methylene blue infusion. A working knowledge of respiratory gasses physiology is desirable. Recognition of a discrepancy between pO$_2$ and SpO$_2$ followed by prompt diagnosis by the use of CO-oximetry is essential in diagnosis. Treating physician should be aware of rebound methemoglobinemia after methylene blue treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Barclay JA, Ziemba SE, Ibrahim RB. Dapsone-induced methemoglobinemia: A primer for clinicians. Ann Pharmacother 2011;45:1103-15.
2. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: Etiology, pharmacology, and clinical management. Ann Emerg Med 1999;34:646-56.
3. do Nascimento TS, Pereira RO, de Mello HL, Costa J. Methemoglobinemia: From diagnosis to treatment. Rev Bras Anestesiol 2008;58:651-64.
4. Jubran A. Pulse oximetry. Crit Care 2015;19:272.
5. Singh S, Sethi N, Pandith S, Ramesh GS. Dapsone-induced methemoglobinemia: “Saturation gap”-the key to diagnosis. J Anaesthesiol Clin Pharmacol 2014;30:86-8.
6. Nitzan M, Romem A, Koppel R. Pulse oximetry: Fundamentals and technology update. Med Devices (Auckl) 2014;7:231-9.
7. Shihana F, Dissanayake DM, Buckley NA, Dawson AH. A simple quantitative bedside test to determine methemoglobin. Ann Emerg Med 2010;55:184-9.
8. Boylston M, Beer D. Methemoglobinemia: A case study. Crit Care Nurse 2002;22:50-5.
9. Collett ND, Geist LJ. Rebound methemoglobinemia: An overlooked diagnosis. Chest 2007;132:732b-3.
10. Ginimuge PR, Jyothi SD. Methylene blue: Revisited. J Anaesthesiol Clin Pharmacol 2010;26:517-20.
11. Sikka P, Bindra VK, Kapoor S, Jain V, Saxena KK. Blue cures blue but be cautious. J Pharm Bioallied Sci 2011;3:543-5.
12. Ramsay RR, Dunford C, Gillman PK. Methylene blue and serotonin toxicity: Inhibition of monoamine oxidase A (MAO A) confirms a theoretical prediction. Br J Pharmacol 2007;152:946-51.
13. Scheinfeld N. Cimetidine: A review of the recent developments and reports in cutaneous medicine. Dermatol Online J 2003;9:4.
14. Topal H, Topal Y. Toxic methemoglobinemia treated with ascorbic acid: Case report. Iran Red Crescent Med J 2013;15:e12718.
15. Rehman HU. Methemoglobinemia. West J Med 2001;175:193-6.