Review Article

The Blood Blues: A Review on Methemoglobinemia

Sheba Rani David, Nora Syahirah Sawal, Muhammad Nur Salam Bin Hamzah, Rajan Rajabalaya
PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Bandar Seri Begawan, Brunei Darussalam

Abstract

Methemoglobinemia is a blood disorder in which there is an abnormal amount of methemoglobin (MetHb) formation, thus unable to release oxygen effectively to body tissues. This is mainly because MetHb is the altered state of hemoglobin (Hb) wherein the ferrous iron of heme has been oxidized to the ferric state. This review paper discusses in detail about the different types of methemoglobinemia and their causes with biochemical pathway and mechanisms. Patients with high MetHb in the blood will appear blue when they have cyanosis but can be cured with the methylene blue solution. However, a proper management should be laid out for strategic treatment. This review will be useful to health-care providers, pharmacists, biochemists, and researchers to understand the basics of methemoglobinemia and its current treatment with guidelines. This review will benefit the readers to understand and will be a ready reference for methemoglobinemia.

Keywords: Hemoglobin, methemoglobinemia, methylene blue

Introduction

Anemia is the condition where the level of red blood cells or the hemoglobin (Hb) concentration in the blood is low, thus disrupting the oxygen concentration in the body tissue due to low oxygen transport.[1] It may have different signs and symptoms based on its causes. While acute anemia presents with hypotension or tachycardia, chronic anemia presents with weakness, fatigue, or pale skin. There are many types of anemia, such as sickle cell, aplastic, hemolytic, iron deficiency, and blood loss and each with different underlying causes. However, there are some types of anemia caused by more than one cause. Hemolytic anemia, for instance, can be caused by the deficiency of enzymes such as glucose-6-phosphate dehydrogenase (G6PD) and pyruvate kinase or by the immune system which destroys the erythrocytes.

A functional anemia like methemoglobinemia is the disruption of the ability to transport oxygen efficiently by the Hb.[2,3] The general color of the skin ranges from pale to pinkish depending on the amount of the Hb and the oxygen supply to the skin. Cyanosis is the bluish or purplish discoloration of the skin due to low oxygen saturation, which is generally called as blue skin. Methemoglobin (MetHb) leads to low oxygen concentration in the blood, leading to cyanosis; thus, it is referred to as blood blues. In addition, methylene blue is generally used to treat methemoglobinemia.

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Methemoglobinemia is the condition where the MetHb level is >1% of the Hb level in the blood.[4-6] The adult normal range of Hb for males and females is 14.0–17.5 g/dL and 12.3–15.3 d/L.[7] Hence, the MetHb for normal adults will be approximately <0.14–0.175 g/dL and 0.12–0.153 g/dL, respectively. The blood would be chocolate brown in color at 70% MetHb fraction. MetHb is formed by the deoxygenation of Hb or due to reactive oxygen species (ROS) such as superoxide and/or peroxide (e.g., hydrogen peroxide) where the iron in the heme group of the Hb is oxidized from ferrous state (Fe^{2+}) to ferric state.[8,9] This oxidized heme group is unable to bind with an oxygen molecule, thus making the erythrocyte unable to transport sufficient amount of oxygen to the body tissue. This leads to the shift of the oxygen dissociation curve to the left as illustrated in Figure 1, thus lowering the oxygen release of other Hb since MetHb lowers the oxygen affinity of other Hb. The presence of MetHb <1% of total Hb in the blood is usually accommodated under normal conditions since the red blood cells have the MetHb reductase

Address for correspondence: Rajan Rajabalaya, PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam, Bandar Seri Begawan BE1410, Brunei Darussalam.
E-mail: rajanmpharm@gmail.com

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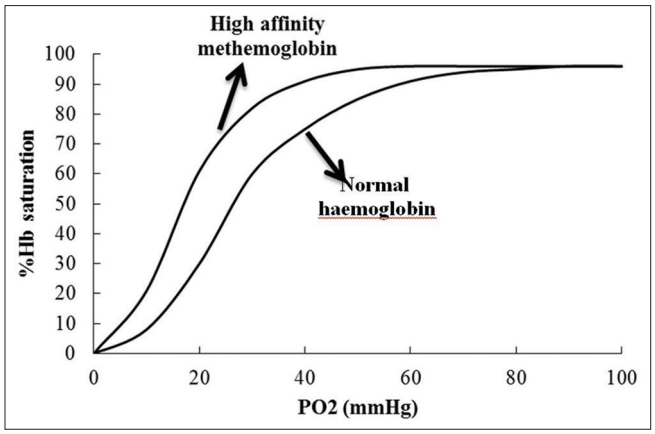


Figure 1: Oxygen–dissociation curve. Methemoglobin has a higher oxygen affinity compared to normal hemoglobin, resulting in the shift of oxygen–dissociation curve toward the left making the release of oxygen difficult. Percentage of haemoglobin (%Hb); partial pressure of oxygen (PO_2)

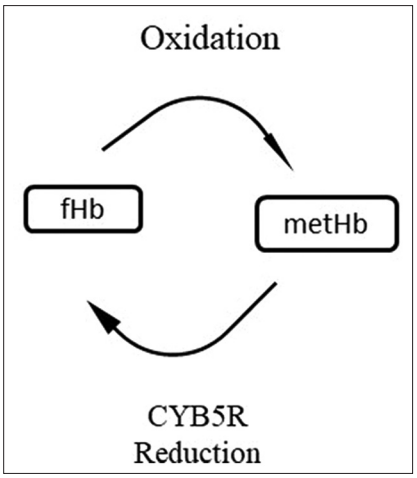


Figure 2: Conversion of fetal hemoglobin to methemoglobin. Methemoglobin is reduced by CYB5R to fetal hemoglobin. The amount of methemoglobin in the blood is exacerbated by the low amount of CYB5R further elevating its amount. Fetal hemoglobin (fHb); methemoglobin (metH); cytochrome B5 reductase (CYB5R)

such as cytochrome B5 reductase (CYB5R, also known as NADH-dependent MetHb reductase or diaphorase-1) and flavin reductases (biliverdin reductase B [BLVRB], nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase, and NADPH-MetHb-diaphorase) to convert the MetHb back to Hb.[4] Flavin reductase is involved in the reduction of ROS to prevent Hb oxidization.

Although some people may tolerate up to 10%–20% of MetHb, cyanosis may occur around 15% MetHb. When MetHb levels are in the range of 20%–45% the person may develop shortness of breath, coughing, headache, lethargy, tachycardia, tissue hypoxia, weakness, and dizziness. When the MetHb level exceeds 45%, the person may develop dyspnea, acidosis, cardiac dysrhythmias, heart failure, seizures, and coma. Severe methemoglobinemia may lead to death if not treated immediately.[2]

Methemoglobinemia can be inherited congenitally or acquired through the consumption or exposure to certain foods and drugs. Inherited methemoglobinemia, a rare gene mutation of the CYB5R3 gene, has two types. Type I is deficient of CYB5R in the erythrocyte only and Type II is deficient in CYB5R, but it generally occurs in all cell types of the patient which can cause severe neurological deficiency.[10] Babies <6 months old may develop methemoglobinemia because they have a low amount of CYB5R to reduce MetHb and easy oxidation of fetal Hb which both lead to high MetHb level in the blood [Figure 2].

Hemoglobin M (HbM) is a variant Hb with a substitution of amino acid in either the alpha or beta part of the Hb. The known HbM variant with methemoglobinemia is the HbM Iwate at position alpha 87 (F8), HbM Hyde Park at position alpha 58 (E7), HbM Boston at position alpha 58 (E7), HbM Saskatoon at position beta 63 (E7), and HbM Milwaukee-I at position beta 67 (E11). All the HbM variants above have the normal tyrosine substituted by histidine, except for HbM Milwaukee-I where the normal valine is substituted by glutamic acid.[6,10,11] The HbM are named according to the place they were first found. They may develop congenital methemoglobinemia due to decreased ability of the enzyme to reduce iron back to its Fe^{2+} state.[12]

Frequently occurring acquired methemoglobinemia is mostly caused by oxidizing drugs, such as nitroglycerine, dapsone, sulfonamides, primacine, phenytoin, phenacetin, and prilocaine. High nitrate-containing food such as beets, spinach, carrots, borage, and chard can induce methemoglobinemia. Most acquired methemoglobinemia is acute as the case is not usually repeated, except for those who need the continuous use of the methemoglobinemia-inducing drugs or unavoidable exposures to the substances. Common examples are in individuals who either drink from the untreated water supply containing a high amount of nitrate and nitrite or in work environments that involve use of pesticide or fungicide.

The complications, mostly due to hypoxia, vary depending on the type of methemoglobinemia; they may include seizure, coma, myocardial infarction, and death. Patients with multiple diseases may attain complications, even death, with lower percentage of MetHb. In congenital methemoglobinemia, the patient may either be asymptomatic or appear to have cyanosis. Moreover, unprogressive condition may worsen when the patients consume drugs inducing methemoglobinemia. The life expectancy is not affected in Type I although in Type II it is severely affected and accompanied by other complications such as neurologic and mental impairment as well as growth malformation. Acquired methemoglobinemia is usually acute but can be life-threatening and may also have other complications such as hemolytic anemia due to drug-induced methemoglobinemia. The disease outcome of methemoglobinemia is positively manageable for moderate cases. However, for critical cases, it is based on the result of the anoxic end-organ damage.[10,11]

Treatment

The drug commonly used to treat methemoglobinemia is methylene blue solution accompanied by supplemental oxygen.[13] The active ingredient is methylene blue trihydrate (3,7-bis (dimethylamino) phenazantionium chloride trihydrate). It is a pro-drug that is converted into leucomethylene blue (colorless) by the flavin reductase in the erythrocytes for it to act as an electron donor. The formation of leucomethylene blue requires NADPH as an electron acceptor. Leucomethylene blue reduces MetHb to Hb while it is converted back to methylene blue, making it recyclable for the next MetHb conversion [Figure 3]. Its rapid action of oxidizing MetHb makes it suitable to treat acute methemoglobinemia. However, methemoglobinemia is further induced at a high concentration of methylene blue due to its oxidizing nature. A person with G6PD deficiency who acquires methemoglobinemia cannot be treated with methylene blue because it induces methemoglobinemia and promotes hemolysis. This is because of the insufficient amount of NADPH to form leucomethylene blue as G6PD is responsible for the production of NADPH in the pentose phosphate pathway. The relationship of G6PD deficiency and MetHb is depicted in Figure 4. A flavin reductase deficient person who acquires methemoglobinemia has no response to methylene blue because of the insufficient amount of reductase to convert it to leucomethylene blue for its therapeutic effect.

For inherited methemoglobinemia, the dose of methylene blue is 50–250 mg per/day orally for a lifetime.[14] For acquired acute methemoglobinemia, 1–2 mg/kg of 1% methylene blue solution is intravenously administered for >20 min and a repeat is required if there is no sufficient response after 1 h. The acquired methemoglobinemia should stop the administration of the drug-inducing methemoglobinemia before treatment with methylene blue to prevent the continuation of MetHb formation and suspected drug–drug interaction such as aniline and dapsone. Most asymptomatic patients are treated with supplemental oxygen and not with methylene blue similar to patients with G6PD deficiency who acquire methemoglobinemia.

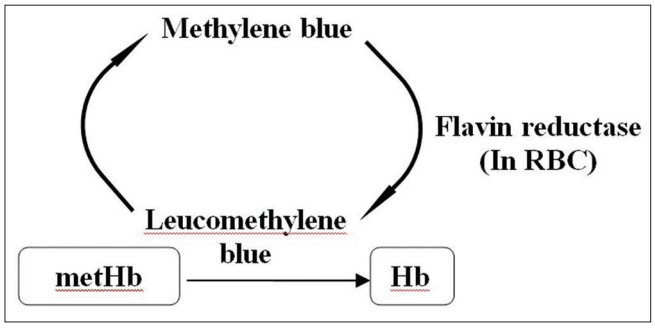


Figure 3: Conversion of methemoglobin to hemoglobin by methylene blue. Methylene blue is converted to leucomethylene blue by flavin reductase, acting as an electron donor. Leucomethylene blue is the active agent that converts methemoglobin to hemoglobin. Hemoglobin (Hb); methemoglobin (MetHb); red blood cells (RBC)

The apparent half-life of methylene blue in the human body is approximately 10 h while the bioavailability is approximately 73% for 200 mg of methylene blue given orally.[14] Furthermore, the plasma–time curve shows that it is well absorbed in the gastrointestinal tract and reaches peak plasma concentration approximately 1–2 h after an oral dose. However, intravenous administration is preferred for acute methemoglobinemia because of its rapid-onset effect. The half-life of intravenously administered methylene blue is estimated about 5–6.5 h [Table 1]. In the body tissue, the methylene blue is rapidly converted into leucomethylene blue. Hence, it is mostly excreted as leucomethylene blue in the urine and eventually becomes green or blue upon standing. It may be excreted via the bile resulting in blue stool. For an oral dose, about 75% of it is excreted in the urine, primarily as leucomethylene blue and few via the bile. A pregnant or lactating woman is not advised to be given methylene blue because there has been no clinical trials and presence of potential suspected adverse effects.

Methylene blue has several adverse effects mainly in the gastrointestinal area if administered orally. The patient may feel nausea, vomiting, diarrhea, abdominal pain, oral dysesthesia, blue saliva, and blue stool. Other common effects are headache, mental confusion, and dyspnea. The patients may experience excessive perspiration and blue urine due to methylene blue administration. At the site of intravenous infusion injection, it is reported that the patient may develop rash with severe burning pain, necrosis, abscess, ulceration, and thrombophlebitis.[15] Excessive dosage of methylene blue may cause blue skin discoloration which can be mistaken for cyanosis or methemoglobinemia.

Methylene blue has some drug–drug interaction especially with serotonergic agents since the patient may develop the

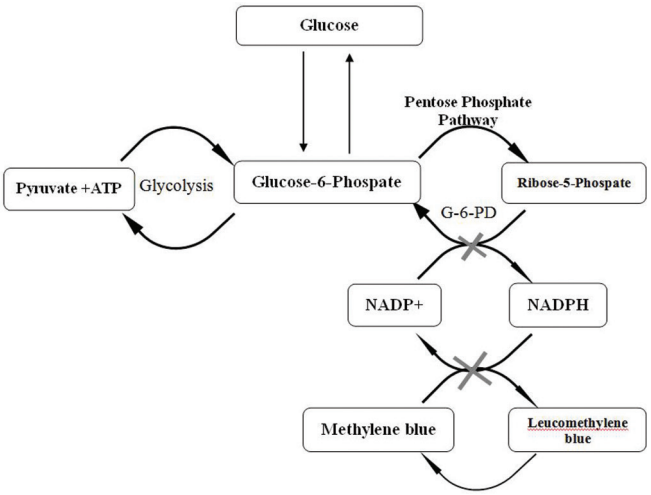


Figure 4: Effect of G6PD deficiency on nicotinamide adenine dinucleotide phosphate production in the pentose phosphate pathway. Patients with G6PD deficiency have reduced production of nicotinamide adenine dinucleotide phosphate in the pentose phosphate pathway. Glucose-6-phosphate dehydrogenase (G6PD); adenosine triphosphate (ATP); nicotinamide adenine dinucleotide phosphate (NADP); reduced form of NADP (NADPH)

signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia, clonus, and incoordination. Hence, either one or both drugs administration should be stopped. Another drug, aniline, especially its intermediates, may block the entry of methylene blue into the erythrocytes, thus making it unable to reduce MetHb which leads to lowered efficacy of methylene blue in its presence. A patient who has methemoglobinemia during the treatment of cyanide poisoning and the patient who acquires acute methemoglobinemia should not be treated with methylene blue since it may cause undesired effects.

If the patient is not responsive or unsuitable for methylene blue therapy, other therapies such as exchange transfusion and hyperbaric oxygen may be considered. These treatments are suitable for patients with G6PD deficiency or HbM variant. Other alternative drugs to treat methemoglobinemia, especially the chronic type, are using ascorbic acid with a dosage of 200–500 mg/day, which may cause formation of stones after long-term consumption or riboflavin with a dosage of 20 mg/day.

Guidelines

Early recognition of methemoglobinemia is very important. The severity of the symptoms will determine the treatment of the methemoglobinemia [Table 2].[11] The patients may probably give a vague and nonspecific presentation. Hence, they should be given initial management such as (i) administration of supplemental oxygen; (ii) working out the etiology that causing the methemoglobinemia; and (iii) removal of the methemoglobinemia-inducing agent. There are several tests which can be conducted for the confirmation of methemoglobinemia, organ functionality, and other disease prevention [Table 3].[16]

Pharmacogenetics

People with G6PD deficiency, the most common genetic variant worldwide, are probably more prone to acquired methemoglobinemia. The drugs for the treatment of G6PD in combination with the food may significantly increase ROS because of the reduced ability to produce sufficient NADPH to protect the red blood cells from ROS to neutralize it. However, methylene blue cannot be used to treat Type I and II G6PD deficiency. Ascorbic acid can be used to treat the methemoglobinemia in G6PD-deficient individuals; however, at high concentration, it may induce hemolysis especially in Type I. Other individuals with enzyme deficiency, such as CYB5R3, catalase (CAT), and reduced glutathione (GSH) deficiency, are at high risk of acquired methemoglobinemia and hemolytic anemia due to increased MetHb in CYB5R3 deficiency and increased ROS in CAT and GSH deficiency. BLVRB-deficient individuals with acquired methemoglobinemia cannot be treated with methylene blue because of the role of BLVRB in the pharmacodynamics of methylene blue.

Table 1: Chemical descriptions of methylene blue

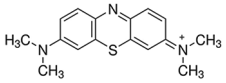
Chemical name	Methylene blue
Molecular formula	$C_{16}H_{18}ClN_3S$
Molar mass	319.85g/mol
Chemical structure	
Half-life upon intravenous (IV) administration	~5-6.5 h
Half-life in human body	~10 h

Table 2: Guidelines for treatment

Types of methemoglobinemia	Treatment
Severe methemoglobinemia	Need emergency therapy (It is life-threatening)
Acute acquired methemoglobinemia	Need to stop administration of inducing agent and emergency therapy
Chronic mild methemoglobinemia	Can be fully asymptomatic with cyanosis or not and no specific therapy required.
Chronic methemoglobinemia	Medications to reduce cyanosis Methylene blue; citric acid; oxygen

Table 3: Diagnostic tests for methemoglobinemia

Diagnostic test
Arterial blood gas (ABG)
Co-oximetry (more accurate) or Pulse oximetry
Potassium cyanide test (metHb and sulfhemoglobin differentiation)
Bedside tests for methemoglobinemia (using filter paper for blood color evaluation or using 100% oxygen to aerate a tube of blood)
CT of the head
Chest radiography (pulmonary and cardiac disease exclusion)
Complete blood count (CBC), reticulocyte counts, lactate dehydrogenase (LDH), indirect bilirubin, haptoglobin
Liver function tests, electrolyte concentrations, blood urea nitrogen (BUN), creatine
Urine pregnancy tests
Heinz body preparation
Serum level of nitrites or inducing drugs
Enzyme assays

Interesting Facts

The family of "Fugates of Troublesome Creek" or "Fugates of Kentucky" was famous for their blue skin color in the 1820s.[17,18] Martin Fugate and his spouse Elizabeth Smith, both carriers of congenital methemoglobinemia, lived in the rural area on the banks of Troublesome Creek, a beautiful area in Appalachian Kentucky.[19] They had seven children, out of which four of them were blue. Since the area they lived was isolated, their children had opted for inter-marriage among relatives in the region causing the recessive gene to be passed to the next generations. However, even though they were blue due to methemoglobinemia, they were entirely healthy and able to live to 60–80 years of their life.

In the 1960s, a young hematologist named Madison Cawein traveled to the Appalachian region, with an aim to cure the blue people of their skin color. She managed to get few of the family members to volunteer in her study. After performing a few tests on the lungs and heart of the volunteer, she began to suspect a rare condition that caused the blood to be blue. Eventually, she managed to find the cause of the disease which was the deficiency of the CYB5R3 enzyme in the blood. She tried to convince the family to take methylene blue as medication to reduce the blue color of the skin. As the coal train and other modern highways started to reach the region, people began to leave the area including the descendants of Fugates, causing the gene to disperse around Kentucky, Ireland, and Finland. Thus, lowering the chances of acquiring the gene for the congenital methemoglobinemia to the next generation.[20]

Conclusion

Methemoglobinemia is not considered as anemia. It is one of the hematological disorders where the Hb cannot function properly. Methemoglobinemia can be congenital or acquired. The chronic congenital methemoglobinemia has no pharmacological treatment while acquired methemoglobinemia needs emergency treatment with methylene blue. However, individuals with HbM and G6PD deficiency are unsuccessful with methylene blue therapy but may cause the reverse effect. Thus, patients with methemoglobinemia should be tested for any other complications that may contraindicate with methylene blue therapy. Patients who are susceptible to methemoglobinemia should be advised to consult with their doctor before taking any new medications and strictly follow the given prescription if the drugs are unavoidable.

Authors contribution

Sheba Rani David was responsible for the idea and draft writing for the manuscript. Muhammad Nur Salam Bin Hamzah was responsible for literature search as well as draft writing for the manuscript. Nora Syahirah Sawal was responsible for formatting and editing the overall manuscript. Rajan Rajabalaya was responsible for the overall supervision of the editing, manuscript writing, as well as for correspondence with the journal.

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Conflicts of interest

There are no conflicts of interest.

References

1. Kucera A, Smith B, Tsu LV. Anemia and the role of the pharmacist. Arizona J Pharm 2014;12:31-5.
2. Khanal R, Karmacharya P, Pathak R, Poudel DR, Ghimire S, Alweis R, *et al.* Do all patients with acquired methemoglobinemia need treatment? A lesson learnt. J Community Hosp Intern Med Perspect 2015;5:29079.
3. Turner MD, Karlis V, Glickman RS. The recognition, physiology, and treatment of medication-induced methemoglobinemia: A case report. Anesth Prog 2007;54:115-7.
4. McDonagh EM, Bautista JM, Youngster I, Altman RB, Klein TE. PharmGKB summary: Methylene blue pathway. Pharmacogenet Genomics 2013;23:498-508.
5. Topal H, Topal Y. Toxic methemoglobinemia treated with ascorbic acid: Case report. Iran Red Crescent Med J 2013;15:e12718.
6. Viana MB, Belisário AR. *De novo* alpha 2 hemoglobin gene (HBA2) mutation in a child with hemoglobin M iwate and symptomatic methemoglobinemia since birth. Rev Bras Hematol Hemoter 2014;36:230-4.
7. Beutler E, Waalen J. The definition of anemia: What is the lower limit of normal of the blood hemoglobin concentration? Blood 2006;107:1747-50.
8. Su YF, Lu LH, Hsu TH, Chang SL, Lin RT. Successful treatment of methemoglobinemia in an elderly couple with severe cyanosis: Two case reports. J Med Case Rep 2012;6:290.
9. Vallurupalli S, Manchanda S. Risk of acquired methemoglobinemia with different topical anesthetics during endoscopic procedures. Local Reg Anesth 2011;4:25-8.
10. Warang P, Kedar P, Sivanandam S, Jothilakshmi K, Sumathi R, Colah R, *et al.* A novel nine base deletion mutation in NADH-cytochrome b5 reductase gene in an Indian family with recessive congenital methemoglobinemia-type-II. Mol Genet Metab Rep 2015;5:44-7.
11. Rehman HU. Methemoglobinemia. West J Med 2001;175:193-6.
12. Abdul Rahaman JA, Ker HB, Yusof M, Hanafi NS, Wong JL. Tuberculosis in adults. Malays Fam Physician 2014;9:34-7.
13. Denshaw-Burke M, DelGiacco E, Curran AL, Savior DC, Kumar M. Methemoglobinemia Treatment & Management. Medscape; 2016. Available from: http://www.emedicine.medscape.com/article/204178-treatment#showall. [Last accessed on 2017 May 03].
14. Schirmer RH, Adler H, Pickhardt M, Mandelkow E. "Lest we forget you – Methylene blue.". Neurobiol Aging 2011;32:2325.e7-16.
15. Methylene Blue Solution for Injection. Medsafe Data Sheet. AFT Pharmaceuticals Ltd.; 2010.
16. Denshaw-Burke M, DelGiacco E, Curran AL, Savior DC, Kumar M. Methemoglobinemia. Medscape; 2016. Available from: http://www.emedicine.medscape.com/article/204178-overview#showall. [Last accessed on 2017 May 03].
17. Gammon K. Can People Have Blue Skin? Live Sci; 2013. Available from: http://www.livescience.com/34410-blue-skin-argyria-methemoglobinemia.html. [Last accessed on 2017 May 03].
18. James SD. Fugates of Kentucky: Skin Bluer than Lake Louise. ABC News; 2012. Available from: http://www.abcnews.go.com/Health/blue-skinned-people-kentucky-reveal-todays-genetic-lesson/story?id=15759819. [Last accessed on 2017 May 03].
19. Lefler L. Blue People in Kentucky: The True Story of the Fugate Family with Blue Skin. Owlcation; 2016. Available from: https://www.owlcation.com/humanities/Blue-People-in-Kentucky-A-True-Story-of-a-Family-with-Blue-Skin. [Last accessed on 2017 May 03].
20. Nickson C. Methylene Blue. Life Fastlane; 2017. Available from: http://www.lifeinthefastlane.com/ccc/methylene-blue/. [Last accessed on 2017 Apr 27].