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REVIEW ARTICLE

A Review of Methemoglobinemia: Pathophysiology, Diagnosis, and Management

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Abstract

Methemoglobinemia is a rare disorder of the blood in which there is an increase in the proportion of hemoglobin present in the oxidized form (methemoglobin). It may be inherited, due either to a deficiency of methemoglobin reductase or to a structural abnormality of hemoglobin, or it may be acquired, usually secondary to exposure to drugs or chemicals that oxidize hemoglobin Nearly 90 compounds have been implicated in the production of Methemoglobinemia, nitrates and aniline derivatives are among the most common agents. Drugs rarely produce clinically significant Methemoglobinemia when given to a normal adult in therapeutic doses, while individuals with methemoglobin reductase deficiency or abnormal hemoglobin may exhibit severe effects as well as overdose. Drugs that may cause Methemoglobinemia include nitrates derivatives (nitrates salt, nitroglycerin), nitrites derivatives (nitroprusside, amyl nitrite, nitric oxide), sulfonamides, dapsone, phenacetin, phenazopyridine, some local anesthetics such as prilocaine, topical anesthetics such as emla cream, benzocaine, antimalarial Observation of asymptomatic individuals for 24 hours may be advisable with exposure to some oxidants drugs which require biochemical transformation before causing Methemoglobinemia.

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INTRODUCTION

Methemoglobinemia is a rare disorder of the blood in which there is an increase in the proportion of hemoglobin present in the oxidized form (methemoglobin). It may be congenital, due either to a deficiency of methemoglobin reductase or to a structural abnormality of hemoglobin, or it may be acquired, usually secondary to exposure to drugs or chemicals that oxidize hemoglobin, and occasionally are secondary to pathologic conditions, such as sepsis, sickle cell crisis, and gastrointestinal infections in children. Drugs have been implicated in the production of Methemoglobinemia, nitrates and aniline derivatives are among the most common agents. Drugs rarely produce clinically significant Methemoglobinemia when given to a normal adult in therapeutic doses, while individuals with methemoglobin reductase deficiency or abnormal hemoglobin may exhibit severe effects as well as overdose. Drugs that may cause Methemoglobinemia include nitrates derivatives (nitrates salt, nitroglycerin), nitrites derivatives (nitroprusside, amyl nitrite, nitric oxide), sulfonamides, dapsone, phenacetin, phenazopyridine, some local anesthetics such as prilocaine, topical anesthetics such as emla cream, benzocaine, antimalarials. Administration of low doses over prolonged periods may lead to chronic methemoglobinemia whereas large doses may lead to an acute effect. The risk Methemoglobinemia associated with oxidizing drugs use is increased in Persons with health problems (a genetic deficiency of G-6-PD or methemogloin reductase, hemoglobin "m", renal failure, anemia, HIV infection), infants (less than three months) due to limited enzyme capacity, elderly, large dose, prolonged therapy, concomitant administration of more than one oxidant drugs, potency of the drugs, route of administration of drugs. Methemoglobinemia may not develop for several hours (e.g, 1 to 10) after exposure to some oxidant's agents. Observation of asymptomatic individuals for 24 hours may be advisable with exposure to some oxidants drugs which require biochemical transformation before causing Methemoglobinemia [1-4].

HISTORY

In the congenital (hereditary) form of the disorder, the hallmark background is the presence of diffuse, chronic, slate gray cyanosis, sometimes present from birth. No evidence of cardiopulmonary disease is available. In spite of the presence of cyanosis, patients with hereditary methemoglobinemia are asymptomatic. Methemoglobinemia is quite suggestive of the failure of 100 percent oxygen to correct cyanosis. Acute methemoglobinemia can be life-threatening and is commonly acquired as a result of toxin or drug exposure. It is necessary, therefore, to obtain a comprehensive history of exposure to methemoglobinemia-inducing substances. Such a history may not always be forthcoming, but when longterm or repetitive exposure may occur, it should always be searched actively. It may be important to consult a toxicologist, especially when introduced to a new

drug, since the list of medications known to cause methemoglobinemia is constantly evolving. A normal methemoglobin fraction is about 1% (range, 0-3%).At methemoglobin levels of 3-15%, a slight discoloration (eg, pale, gray, blue) of the skin may be present. Apart from moderate cyanosis, patients with a 15-20 percent methemoglobin level may be generally asymptomatic. Infants and children may experience methemoglobinemia, caused by chronic dehydration and diarrhea, at methemoglobin fractions greater than 70%, death usually occurs in combination with metabolic acidosis. The consumption of water from wells polluted with excess nitrates and exposure to local anesthetics in teething gels are the causes of unintended toxin exposure that must be addressed in infants and children. In a detailed history, these considerations may often be elicited.[5]

It is essential to explain any known family history of methemoglobinemia or glucose-6-phosphate dehydrogenase (G6PD) deficiency. Even patients who are heterozygous for defects of the methemoglobin reductase enzyme are prone to low doses of methemoglobinemiaresulting oxidant medications. The existence of symptoms of the gastrointestinal (GI) system (e.g., nausea, vomiting, or diarrhea) may indicate the likelihood of a toxic material being ingested. In the case of anemia, the clinical symptoms of methemoglobinemia are compounded. Navajo have been found to have an elevated prevalence of the disease. [6-8]

LITERATURE SURVEY

A literature search using the terms methemoglobinemia and co-oximetry was performed in the PubMed and MEDLINE databases. Multiple potentially relevant studies were reviewed and considered for inclusion. References from selected articles were also searched. Inclusion criteria comprised, but were not limited to, articles published within the past 10 years regarding acquired methemoglobinemia related to local anesthetics or environmental agents.[9-10]

CASE REPORTS

Case 1:

A 22-year-old woman presented to the emergency department with post-tonsillectomy bleeding. Her vital signs were within normal limits and included an oxygen saturation of 99% on room air. The patient was promptly evaluated by the on-call otorhinolaryngologist. Following multiple applications of nonmetred doses of 20% benzocaine topical aerosol spray, localized cauterization was performed. After hemostasis was achieved, the patient was transferred back to the emergency department for observation and intravenous rehydration. Forty-five minutes later, the patient was noted to be profoundly cyanotic and diaphoretic, with a room air oxygen saturation of 89%. Despite use of a non-rebreathing face mask, the patient remained hypoxic, with oxygen saturations of around 88%. A portable chest x-ray scan taken immediately showed no relevant findings, an electrocardiogram had normal findings,

and both blood pressure and heart rate remained within normal limits. Arterial blood gas was measured expeditiously; the blood was noted to be chocolate brown in colour, with a pH of 7.38, a Pco2 of 37.2 mm Hg, a bicarbonate level of 24 mmol/L, and a Po2 of 33.6 mm Hg. Portable co-oximetry was then performed, which identified a methemoglobin level of 23%. An infusion of 100 mg of methylene blue was given for 5 minutes, with immediate improvement in the patient's oxygen saturation. Repeat co-oximetry showed a methemoglobin level of 12%, and a second 100-mg dose of methylene blue was administered. Within minutes, the patient's colour had returned to normal and her oxygen saturation was 100% on room air. The patient was subsequently admitted to the intensive care unit for close monitoring with continuous pulse oximetry and serial methemoglobin level checks. During the next 18 hours the patient remained hemodynamically stable, with good oxygenation on room air and a normal methemoglobin level.

Case 2 :

A 32-year-old man presented to the emergency department with acute onset of light-headedness, nausea, and paresthesia of the upper extremities. Symptoms started approximately 1 hour after drinking a large amount of "metallic-tasting" water from a fountain located at the Warrior Transition Battalion building in which he resided. Initial vital signs were normal except for a room air oxygen saturation of 92% via pulse oximetry. Physical examination findings were notable for acrocyanosis, and he was given 2 L of oxygen via nasal cannula. Portable co-oximetry revealed a methemoglobin level of 15%. Arterial blood gas was measured and showed a pH of 7.40, a Pco2 of 39.9 mm Hg, a bicarbonate level of 25 mmol/L, and a Po2 of 103.0 mm Hg. Additional bloodwork results were unremarkable, and the patient was subsequently admitted for overnight observation. Because the patient was no longer symptomatic, methylene blue was not administered and his room air oxygen saturation steadily improved with supplemental oxygen.2 The following morning, his methemoglobin level was 1.3% and he remained asymptomatic. Subsequent analysis of the drinking water revealed high levels of nitrates.[11-12]

TYPES OF METHEMOGLOBINIMEA

Methemoglobinemia can result from either congenital or acquired processes.

CONGENITAL:

Congenital/hereditary forms of methemoglobinemia are either caused by enzyme deficiency (autosomal recessive defects of the cytochrome b5 reductase enzyme) or by autosomal dominant mutations, called hemoglobin M, in the genes that code for globin proteins. It is characterized by a decrease in methemoglobin's enzymatic reduction back to functional hemoglobin. Hemoglobin M disease patients are normally asymptomatic and should be consulted as to the benign aspects of their condition. There is no suitable alternative available if care is needed for this disorder. Patients with congenital methemoglobinemia can have 20-40%

methemoglobin levels.They are generally cyanotic from birth, but with normal growth, they are asymptomatic. Siberian Yakuts, Athabaskans, Eskimos, and Navajo have been found to have an elevated prevalence of the disease. [13-15]



Figure 1: Congenital methemoglobinemia

ACQUIRED

Acquired methemoglobinemia is more prevalent and results from direct oxidizing agent exposure. It can be fatal and generally results from the ingestion of specific medications or agents that cause methemoglobinin production to increase. Nitroglycerine, dapsone, sulfonamides, phenytoin, phenacetin, and local anesthetics are typical medicines with oxidizing impact. Many agrochemical compounds contain a solvent that can result in serious, even fatal, methemoglobinemia. Most of these compounds do not have compositional specifics and can lead to extreme methemoglobinemia. Neonates and infants are at a higher risk of methemoglobin accumulation when exposed to such medications due to underdeveloped methemoglobin reduction mechanisms.[16-18]



Figure 2: Acquired methemoglobinemia

PHYSICAL PROPERTIES OF METHEMOGLOBIN

Hemoglobin molecules contain iron within a porphyrin heme structure. The iron in hemoglobin is normally found in the Fe^{++}state. The iron moiety of hemoglobin can be oxidized to the Fe^{+++} state to form MHb.10 Once MHb is formed, the molecule loses its ability to carry molecular oxygen. Because RBCs are bathed in oxygen, a certain amount of physiologic MHb formation occurs continuously.10Several endogenous reduction systems exist to maintain MHb in the reduced state, and in normal individuals only about 1% of total hemoglobin is MHb at any given time.10Because oxidized hemoglobin is incapable of carrying oxygen (or carbon dioxide), excess MHb leads to cyanosis, impaired aerobic respiration, metabolic acidosis, and in severe cases, death. Hemoglobin is a tetrameric molecule, and the complete oxidation to MHb would represent a 4-electron loss. However, under conditions of oxidative stress, partial oxidation of the individual subunits predominates, and as such 8 different dimers may

exist (there are 4 subunits to hemoglobin (a2 b2) and 2 iron valences (Fe++and Fe+++); thus, 8 different states can exist.1,10 The nonoxidized portions of these hybrid valence forms have a high affinity for oxygen and shift the oxygen dissociation curve to the left.10 In other words, any oxygen that is carried by the nonoxidized hemoglobin subunits is held on to more tightly and poorly released to tissues. This property is important clinically. For example, a patient with 35% MHb has a theoretical oxygen-carrying capacity of 65% of his or her hemoglobin. Functionally, however, this is not the case, because allosteric changes to the hemoglobin molecule cause oxygen to bind more tightly in the partially oxidized hemoglobin molecules. This increased affinity causes a left shift in the hemoglobin-oxygen saturation curve. Oxidation also results in a net positive charge to the MHb molecule compared with normal hemoglobin. MHb has high affinity for negative anions such as cyanide, fluoride, or chloride (CN–, F–, and Cl–) as opposed to the uncharged binding ligands (CO_2, CO, and O_2) of normal hemoglobin. [19-25]

SYMPTOMS

A literature search using the terms methemoglobinemia and co-oximetry was performed in the PubMed and MEDLINE databases. Multiple potentially relevant studies were reviewed and considered for inclusion. References from selected articles were also searched. Inclusion criteria comprised, but were not limited to, articles published within the past 10 years regarding acquired methemoglobinemia and methemoglobinemia related to local anesthetics or environmental agents. The symptoms based on the concentration of Methemoglobinemia is given in the Table: 1 [26-27]

Table: 1 Symptoms of Methemoglobinemia

Concentration of Methemoglobin	Symptoms
0-3%	No symptoms
10-20%	Cyanosis, Chocolate brown blood
20-50%	Dyspnea, Exercise Tolerence, Fatigue, Dizziness, Tachycardia.
>50%	CNS hypoxia, Seizure, Coma, Dysrhythmias, Ischemia, Tachypnea, Metabolic acidosis.
>70%	Severe hypoxia, death

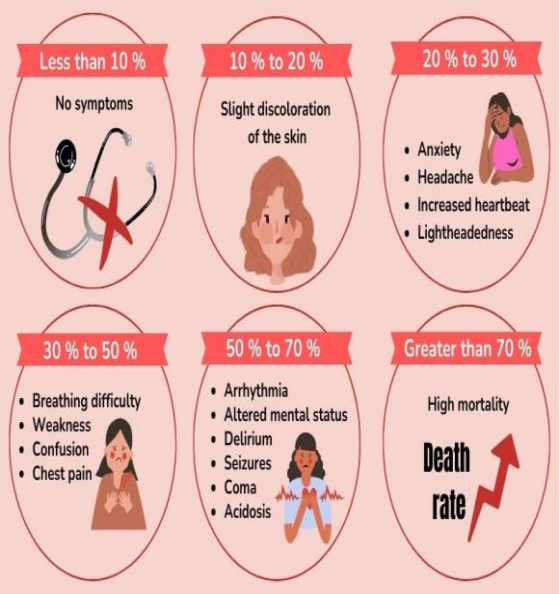


Figure 3: Signs and Symptoms of Methemoglobinemia

MECHANISM OF ACTION

In normal persons, the methemoglobin (met Hgb) levels are kept below 1% by an nicotinamide adenine dinucleotide phosphate (NADPH) dependent methemoglobin reductase enzyme which is effective in reducing methemoglobin back to the ferrous state, ((NADPH) pathway, a second enzymatic system which reduces methemoglobin to hemoglobin, is directly dependent on both the activity of glutlathione and glucose-6-phosphate dehydronease). However hereditary deficiencies in the activity of this enzyme result in chronic methemoglobin levels of 40% to 50%. Methemoglobin is formed by oxidation of the ferrous iron (Fe(2+)) of hemoglobin to ferric (Fe(3+)) form by oxidizing chemical or drugs this reaction impairs the ability of hemoglobin to transport oxygen and carbon dioxide, leading to tissue hypoxemia and in severe cases, death.

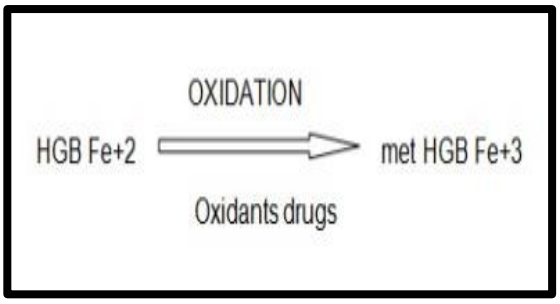


Figure 4: Oxidation of Hemoglobin

Oxidizing agents can be divided into those that directly oxidize hemoglobin to methemoglobin and those that indirectly oxidize hemoglobin. Direct oxidizers react directly with hemoglobin to form MHb. Indirect oxidizers are actually powerful reducing agents that reduce oxygen to the free radical O2–, or water to H2O2, which in turn oxidizes hemoglobin to MHb. Many oxidant drugs not directly oxidize hemoglobin to methemoglobin, but require biochemical transformation to toxic metabolites which cause methemoglobin, example, Dapsone is metabolized by the cytochrome p-450 system to free radical hydroxylamine, which reacts with O2 to form oxygen free radicals which oxidize ferrous of hemoglobin to form methemoglobin. Aniline is s a potent inducer of methemoglobinemia and hemolysis, but it coverted first to phenylhydroxyamine that is oxidized to nitrosobenzene by Hgb (Fe(II)) and oxygen. The nitrosobenze is subsequently reduces by a NADPH flavin reductase back to aniline, using NADPH derived from glucose-6-phoshate dehydrogenas and the hexose monophosphate shunt. Alternatively, glutathione can be used as a source of reducing power Aniline and nitros-derivatives are transformed into phenylhydroxylamines by hepatic mixed function oxidases, and then can become inducers. Such bioactivation is important for the toxic effects of dapsone and sulfamethoxazole (the sulfa component in trimethoprim-sulfamethoxazole) probably via the formation of hydroxylamines. The dapsone hydroxylamine was the more potent in forming methemoglobin more potent in forming Medical Group Analgesic Atiperetics Drugs and methemoglobin and consuming glutathione compared to the sulfamethoxazole hydroxyl amine paralleling the in vivo findings Along with the production of methemoglobin reducing power in the cell is depleted. The depletion is explained by the

recycling mechanism and once the glutathione is depleted, the continued formation of methemoglobin should stop. Because of the variability in metabolism among individulas, and rate of absorption or enteroheptic recirculation of the drugs not every patient may develop methemoglobinemia when exposed to such drugs. This may explain why not everyone who ingests oxidant drug develops methemoglobinemia, only those who metabolize a significant amount of parent drug to the toxic metabolite develop methemoglobimemia. This may explain why not every child who ingests benzocaine develops MHb. Only those who metabolize a significant amount of parent drug to the toxic metabolite develop methemoglobinemia [28-30].

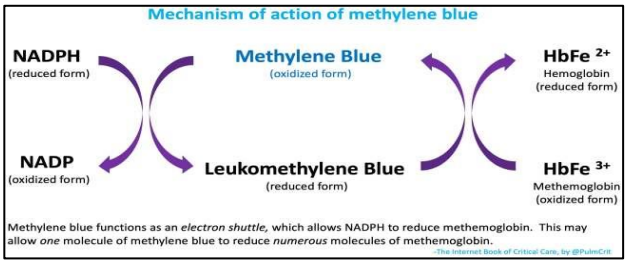


Figure 5: Mechanism of action of methylene blue

Drugs Induced Methemoglobinemia

Methemoglobinemia may occur as a result of medication overdoses or poisoning, but may also occur at standard doses, particularly in individuals with partial deficiencies of cytochrome b5R. Various drugs are capable of inducing methemoglobinemia following inhalation, skin absorption, or ingestion. Signs and symptoms of methemoglobinemia may be delayed several hours because some drugs do not directly produce methemoglobinemia, but require biochemical transformation to toxic metabolites which cause methemoglobinemia. Adminstration of low doses over prolonged periods may lead to chronic methemoglobinemia whereas large doses may lead to an acute affect methemoglobinemia. Over the years, numerous case reports have established that either the ingestion of or the exposure to skin and or mucous membranes can lead to an adverse reaction which causes methemoglobinemia. Most of the medications directly oxidize hemoglobin to methemoglobin, while others indirectly oxidize hemoglobin to methemoglobin by reducing free oxygen to a superoxide free radical. [31-32] (Table 1 summarizes the drugs that induce methemoglobinemia) [31-34].

COMPLICATIONS

Methemoglobinemia can be chronic or acute. The physiological level in the blood of methemoglobin is 0 to 2 percent.2 Methemoglobin concentrations of 10 to 20 percent are well tolerated, although symptoms are frequently associated with levels above this. Levels above 70% can trigger death. The rapidity of its formation often depends on symptoms. Many patients with lifelong methemoglobinemia are asymptomatic, although there may be serious symptoms in patients exposed to medications and toxins that abruptly experience the same levels of methemoglobinemia. There is cyanosis in small infants with methemoglobinemia that fails to respond to supplemental oxygen. Cyanosis commonly occurs shortly after birth in those with congenital methemoglobinemia. At

methemoglobin levels of 30 percent or more, dyspnea, nausea, and tachycardia occur. As methemoglobin levels reach 55 percent, lethargy, stupor, and declining consciousness occur. Higher levels of cardiac arrhythmias and circulatory failure may lead to Drug-induced methemoglobinemia, especially with exposure to dapsone, sulfasalazine, or phenacetin, may be accompanied by hemolytic anemia. Heinz bodies (precipitated hemoglobin or globin subunits due to hemoglobin denaturation in erythrocytes) and scattered red blood cells characterize anemia. Acute intravascular hemolysis can sometimes lead to renal failure. Jaundice hemolytic anemia can also be a characteristic of hemoglobin MSaskatoon and hemoglobin MHyde Park, rare forms of hemoglobin associated with hereditary methemoglobinemia and identified by where they were detected. [35]

DIFFERENTIAL DIAGNOSIS

Cyanotic congenital heart disease is included in the differential diagnosis of methemoglobinemia in small infants, especially when right to left shunting is present. Children with cyanotic congenital heart disease receiving supplemental oxygen have low partial oxygen pressure and low measured oxygen saturation, however, despite cyanosis and normal calculated oxygen saturation, children with methemoglobinemia have high partial oxygen pressure. Methemoglobinemia should be separated from sulfhemoglobinemia in older children. The insertion of a sulfur molecule into the heme moiety leads to sulfhemoglobinemia. Sulfhemoglobinemia can also be caused by most drugs, especially sulfonamides and phenacetin, that produce methemoglobinemia, although this condition is less common than methemoglobinemia.[36] The symptoms appear to be milder than in methemoglobinemia patients. The diagnosis is confirmed by either spectrophotometry or gas chromatography-mass spectrometry of elevated levels of sulfhemoglobin, Sulfhemoglobinemia does not respond and is tolerant of methylene blue therapy. Exchange transfusion can be useful in extreme cases.[37] Methemoglobin and sulfhemoglobin can be separated by the potassium cyanide examination. Methemoglobin becomes bright red after the addition of a few drops of potassium cyanide, but sulfhemoglobin stays dark brown. This is due to the attachment of cyanide to methemoglobin, creating cyanomethemoglobin, which has a bright red hue. Sulfhemoglobin, on the other hand, is inert and does not bind cyanide. Because of NADH cytochrome b5 reductase deficiency from hemoglobin M disorder, family history is typically helpful in separating methemoglobinemia. The existence of hemoglobin M is indicated by cyanosis in successive generations; normal parents but potentially affected siblings mean the presence of deficiency of NADH cytochrome b5 reductase.[38]

DIAGNOSIS

Blood containing elevated methemoglobin levels tends to be chocolate brown. Despite life-threatening methemoglobinemia, subjects with methemoglobinemia may have normal partial oxygen pressure levels. Saturation levels of oxygen,

measured by a pulse oximeter, are wrongly elevated. An elevated level of methemoglobin is observed in methemoglobinemia due to drug exposure, but the activity of NADH cytochrome b5 reductase is normal. The function of the enzyme is less than 20 percent average in inherited type II methemoglobinemia. Hemoglobin M may be distinguished by its absorption spectrum in the range of 450 to 750 nm from the methemoglobin formed from hemoglobin A. For the separation of hemoglobin Melectrophoresis at pH 7.1 is most useful.[39]

CLINICAL FEATURES

Methemoglobinemia can be chronic or acute. The physiological amount in the blood of methemoglobin is 0 percent-2 percentNormal healthy patients will tolerate 10 percent to 20 percent methemoglobin levels, but at levels above this, symptoms grow. Levels of methemoglobin above 70 percent. While survival with a methemoglobinemia (MetHb) level of 81 percent-91 percent may be fatal, symptoms also depend on the rapidity of methemoglobin formation. Most patients with congenital/hereditary methemoglobinemia remain asymptomatic, but highly symptomatic may be patients who are exposed to medications and toxins resulting in acquired methemoglobinemia. [40-42]

TREATMENT

Methylene blue solution followed by supplemental oxygen is the treatment widely used to treat methemoglobinemia. Methylene bluetrihydrate (3,7-bis(dimethylamino) phenazantionium chloride trihydrate) is the active ingredient. It is a pro-drug that the flavin reductase in the erythrocytes converts to leucomethylene blue (colorless) for it to serve as an electron donor. As an electron acceptor, the formation of leucomethylene blue requires NADPH. When converting back to methylene blue, Leucomethylene blue reduces MetHb to Hb, rendering it recyclable for the next conversion to MetHb. It is suitable to treat acute methemoglobinemia due to its rapid action of oxidizing MetHb. However, due to its oxidizing nature, methemoglobinemia is further induced at a high methylene blue concentration.[43]

Methylene blue does not treat a person with G6PD deficiency who acquires methemoglobinemia because it causes methemoglobinemia and encourages hemolysis. As G6PD is responsible for generating NADPH in the pentose phosphate pathway, this is because of the inadequate amount of NADPH to form leucomethylene blue. The correlation between G6PD deficiency and MetHb is seen. Due to the inadequate amount of reductasto transform it to leucomethylene blue for its therapeutic effect, a flavinreductase deficient person who acquires methemoglobinemia has no response to tomethylene blue. For inherited methemoglobinemia, the dosage of methylene blue for a lifetime is 50-250 mg per/day orally.

For acquired acute methemoglobinemia, 1-2 mg/kg of 1% methylene blue solution is administered intravenously for >20 minutes, and repetition is needed if an appropriate response after 1 h is not present. To avoid the continuation of MetHb formation and suspected drug-drug interaction such as aniline and dapsone, acquired methemoglobinemia can stop the administration of drug-inducing methemoglobinemia until treatment with methylene blue. Many asymptomatic patients are treated with supplemental oxygen and not with methylene blue, similar to those treated with methemoglobinemia in patients with G6PD deficiency. The apparent half-life of methylene blue in the human body is approximately 10 h, whereas bioavailability for 200 mg of methylene blue is approximately 73 percent. In addition, the plasma-time curve indicates that it is well absorbed in the gastrointestinal tract and achieves peak plasma concentration after an oral dose of approximately 12 hours.

Intravenous administration is favored for acute methemoglobinemia because of its rapid-onset effect. The half-life of methylene blue administered intravenously is calculated to be about 5-6.5 h. Methylene blue is quickly transformed into leucomethylene blue in the tissue of the body. As a result, it is mainly excreted in the urine as leucomethylene blue and finally becomes green or blue on standing. It can be excreted through the blue stool arising from the bile. Around 75% of it is excreted in the urine for the oral dose, mainly as leucomethylene blue and few through the bile. Methylene blue is not intended to be given to a pregnant or lactating woman because there have been no clinical trials and possible alleged harmful effects have been identified. Methylene blue has some adverse effects if administered orally, mostly in the gastrointestinal region. Nausea, vomiting, diarrhea, stomach pain, oral dysesthesia, blue saliva, and blue stools may be felt by the patient. Headaches, mental confusion, and dyspnea are other typical symptoms. Due to the administration of methylene blue, patients may experience excessive transpiration and blue urine.

It is recorded that the patient may develop extreme burning pain, necrosis, abscess, ulceration, and thrombophlebitis at the site of intravenous infusion injection. Excessive methylene blue may dose causes blue skin discoloration that may be mistaken for cyanosis or methemoglobinemia. Signs were cognitive dysfunction, hyper pyrexia, hyperreflexia, clonus. Thus, the administration of either one or both medications should be avoided. Another drug, aniline, especially its intermediates, can block the entry into the erythrocytes of methylene blue, rendering it unable to reduce MetHb, which in its presence contributes to a reduction in the efficacy of methylene blue.Methylene blue should not be treated in patients who have methemoglobinemia during the treatment of cyanide poisoning and in patients who have acute methemoglobinemia, as it may cause adverse results.Other treatments such as exchange transfusion and hyperbaric oxygen can be considered if the patient is unresponsive or unsuitable for methylene blue therapy. For patients

with G6PD deficiency or HbM variant, these therapies are sufficient. Other alternative medicines for methemoglobinemia therapy, particular, ascorbic acid with a dosage of 200-500 mg/day, which may induce stone formation after long-term ingestion, or riboflavin with a dosage of 20 mg/day, is used in the chronic kind. [44]

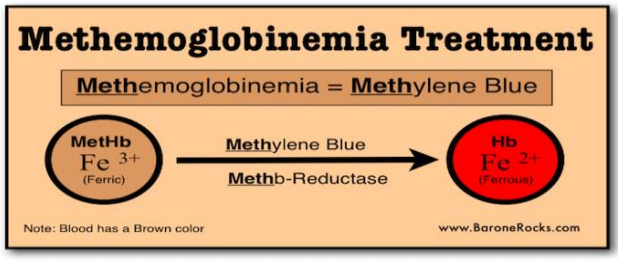


Figure 6: Methemoglobinemia Treatment

CONCLUSION

It is not considered that methemoglobinemia is anemia. It is one of the hematological conditions in which Hb is unable to operate properly. There may be congenital or acquired methemoglobinemia. There is no pharmacological cure for chronic congenital methemoglobinemia, while acquired methemoglobinemia requires methylene blue emergency treatment. However, with methylene blue therapy, people with HbM and G6PD deficiency are ineffective, but the reverse effect can be induced. Any other risks that could contraindicate methylene blue therapy should also be tested in patients with methemoglobinemia. Patients prone to methemoglobinemia should be advised to contact their physician before taking any new drugs and, if the medications are unavoidable, strictly follow the prescription provided.

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