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Review Article

Drug Induced Methemoglobinemia

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Abstract

Methemoglobinemia is a rare disorder of the blood in which there is an increase in the proportion of hemoglobin (Hb) present in the oxidized form (methemoglobin - mHb). Methemoglobinemia (congenital or acquired) occurs when red blood cells (RBCs) contain mHb at higher levels exceeds 1%, resulting in decreased oxygen availability to the tissues. This mini-review updates recent insights into some oxidative drugs that induce methemoglobinemia.

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 – mHb). It may be congenital, due either to a deficiency of mHb reductase or to a structural abnormality of Hb, or it may be acquired, usually secondary to exposure to drugs or chemicals that oxidize Hb, and occasionally it is secondary to pathologic conditions, such as sepsis, sickle cell crisis, and gastrointestinal infections in children.

There are two forms of inherited methemoglobinemia. The first form is passed on by both parents. This form usually does not have the condition themselves, but they carry the gene that causes the condition. It occurs when there is a problem with cytochrome b5 reductase enzyme. While, the second form is called hemoglobin M disease. It is caused by defects in the hemoglobin protein itself. Only one parent needs to pass on the abnormal gene for the child to inherit the disease. On the other hand, acquired methemoglobinemia is more common and occurs in some people after they are exposed to certain chemicals and drugs, including: anesthetics, benzene, antibiotics and nitrites [1,2]

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 mHb reductase deficiency or abnormal Hb may exhibit severe effects as well as overdose. Drugs that may cause methemoglobinemia include nitrate derivatives (nitrates salt, nitroglycerin), nitrites derivatives (nitroprusside, amyl nitrite, nitric oxide), sulfonamides, dapsone, phenacetin, phenazopyridine, some local anesthetics such as prilocaine, and topical anesthetics such as emla cream, benzocaine & antimalarial. Administration of low doses over prolonged periods may lead to chronic methemoglobinemia whereas large doses may lead to an acute effect [3-6].

The risk methemoglobinemia associated with oxidizing drugs use is increased in people with health problems (a genetic deficiency of G6PD or mHb reductase, renal failure, anemia, HIV infection), infants who less than three months due to limited enzyme capacity, elderly, large dose, prolonged therapy, concomitant administration of more than one oxidative drug, potency of the drugs, and the route of administration of drugs. Observation of asymptomatic individuals for 24 hours may be advisable after exposure to some oxidative drugs which require biochemical transformation before causing methemoglobinemia [7,8].

Pharmacology

In normal people, mHb levels are kept below 1% by an nicotinamide adenine dinucleotide phosphate (NADPH) dependent methemoglobin reductase enzyme which is effective in reducing mHb back to the ferrous state, NADPH pathway, a second enzymatic system which reduces mHb to Hb, is directly dependent on both the activity of glutlathione and glucose-6-phosphate dehydronease (G6PD). However, hereditary deficiencies in the activity of this enzyme can result in chronic mHb levels of 40% to 50%. mHb is formed by oxidation of the ferrous iron ($fe^{(2+)}$) of Hb to ferric ($fe^{(3+)}$) form by oxidizing chemicals or drugs and this reaction impairs the ability of Hb to transport oxygen and carbon dioxide, leading to tissue hypoxemia and in severe cases, even death.

Oxidizing agents can be divided into those that directly oxidize Hb to mHb, and those that indirectly oxidize Hb. Direct oxidizers react directly with Hb to form mHb. Indirect oxidizers are actually powerful reducing agents that reduce oxygen to the free radical O^{2-}, or water to H_2O_2, which in turn oxidizes Hb to mHb.

Many oxidant drugs do not directly oxidize Hb to mHb but require biochemical transformation to toxic metabolites which cause mHb. For example, Dapsone is metabolized by the cytochrome p450 system to free radical hydroxylamine, which reacts with O_2 to form oxygen free radicals which oxidize ferrous of Hb to form mHb. Aniline is a potent inducer of methemoglobinemia and hemolysis, but it is converted first to phenylhydroxyamine which is then oxidized to nitrosobenzene by Hb (Fe (II) and oxygen). The nitrosobenzene is subsequently reduced by a NADPH flavin reductase back to aniline, using NADPH derived from G6PD 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 bio activation 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 is more potent in forming mHb and consuming glutathione compared to the sulfamethoxazole hydroxyl amine, paralleling in vivo findings. Along with the production of mHb, reducing power in the cell is depleted.

The depletion is explained by the recycling mechanism, and once glutathione is depleted, the continued formation of mHb should stop [9]

Because of the variability in metabolism among individuals, 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 an oxidant drug develops methemoglobinemia, whilst only those who metabolize a significant amount of parent drug to the toxic metabolite develop methemoglobimemia. This may explain for example why not every child who ingests benzocaine develops mHb. Only those who metabolize a significant amount of parent drug to the toxic metabolite actually develop methemoglobinemia [3,10]

Links between Drugs and Methemoglobinemia

Methemoglobinemia may occur as a result of medication overdose or poisoning, but may also occur at standard doses, particularly in individuals with partial deficiencies of cytochrome b5R [11,12]. 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. Administration 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 ingestion, or exposure to skin or mucous membranes, can lead to an adverse reaction which causes methemoglobinemia. Most of the medications causing this directly oxidize Hb to mHb, while others indirectly oxidize Hb to mHb by reducing free oxygen to a superoxide free radical (Table 1 summarizes the drugs that induce methemoglobinemia) [5,10,13,14]

Medical Group	Drugs
Analgesic & Antipyretics	**Examples:** Acetaminophen Antipyrin (Antipyrin & Benzocaine)
Anti-convulsants	**Examples:** Phenobarbital Phenytoin
Anti-Infective Drugs Anti-microbial Anti-malarial	**Examples:** **Sulfonamide:** Cotrimcxazole (Sulfamethoxazole-Trimethoprim) - **Solfon:** Dapsone Nitrofurantoin Para-Aminosalicylic Acid - Rifampin
Hormones	Flutamide
Psychotherapeutic	**Examples:** Phenelzine
Vasodilators Nitrate Derivative Nitrite Derivative	**Examples:** Isosorbide Dinitrate, Silver Nitrate, Sodium Nitrate, Nitrate Salt Sodium Nitrite Nitric Oxide
Vitamins	**Examples:** Menadione (Vitamin K3)
Miscellaneous Topical Anesthetic Local Anesthetics Anti-infective Topical	**Examples:** Benzocaine Amethocain, Articaine, Benzocain, Cetacaine Carbol -Fuchsin Topical Solution (Resorcinol, Basic Fuchsin Cetrimide

Table 1: Drugs that induce methemoglobinemia

Oxidizing agents accelerate 100 to 1,000 times the oxidation of Hb, and eventually overwhelm the capacity of reducing endogenous systems; they include several drugs, intoxication with pesticides, herbicides, and fertilizers 3, automobile exhaust fumes, and industrial chemicals [5,6]

Predisposing Factors that Lead to Drug-Induced Methemoglobinemia

Potency of the oxidizing agent

Strongly oxidizing drugs produce methemoglobinemia more than weak oxidizing drugs. Drugs containing an aniline group, a nitroso group, or which metabolize to nitroso or aniline or hydroxylamine metabolites induce methemoglobinemia more than other drugs, e.g. phenacetin is metabolized to nitroso compounds (N-or-2-OH phenetidine) which can cause methemoglobinemia after overdose. Although acetaminophen active metabolite of phenacetin, acetaminophen does not cause mHb formation because of the absence of nitroso metabolites; however, methemoglobinemia has been reported in one patient after acetaminophen dose but unconfirmed by other studies.

Phenazopyridine - in vivo 50% of phenazopyridine is metabolized to aniline. Phenazopyridine may induce methemoglobinemia after therapeutic use and overdose (aniline produced by 200 mg of phenazopyridine three times a day exceeds the 35 mg maximal allowable dose of aniline). Nitrate derivatives, which are relatively nontoxic, can be reduced to nitrite derivatives (more potent methemoglobin inducing agents) in the gut by bacteria such as pseudomonas areuginosa, bacillus subtilis, aerobacter cloacae, Escherichia spp, and salmonella. The world health organization limits daily intake of nitrate to 5 mg/kg and nitrite 0.4 mg/kg.

Local injection or topical administration of anesthetics induce methemoglobinemia, and prilocaine more commonly induces methemoglobinemia than other local anesthetics; this effect is due to the metabolism of prilocaine to an aniline like structure and also to o-toluidine, both of which are known inducers of methemoglobin. A report from the University of Montreal reviewed 242 published episodes of local anesthetic-related methemoglobinemia and presented recommendations for prevention and treatment. Benzocaine and prilocaine were involved in 66% and 28% of the cases, respectively, and lidocaine in 5%. A majority of these cases involved a procedure conducted outside the operating room and 6% involved an over the counter medication. In a retrospective series of 138 cases at 2 teaching hospitals, it was found that dapsone was the most common cause of acquired methemoglobinemia and which accounted for 42% of all cases (ref15).

Concomitant administration more than one oxidative drug

Co-administration of more than one of oxidative drug, especially when both drugs are strong oxidative drugs may increase formation of toxic metabolites or enhance oxidation Hb if the drugs not require biochemical transformation. Examples including: administration of primaquine to a patient with HIV infection within 24 hours of last dose of dapsone can produce clinically significant methemoglobinemia. Emla cream (prilocaine-lidocaine) or aurlgan (antipyrin & benzocaine has induced methemoglobinemia in an infant of less than 3 months. The mHb level increased when isosorbid dinitrate and nitroglycerin ointment were given in combination.

Benzocaine containing over the counter products with miconazole nitrate vaginal suppositories have induced clinical significant methemoglobinemia in females. Methemoglobinemia has been reported in infants after 36 hours of administration a topical anesthetic cream containing 5% benzocaine and 2% resorcinol for the treatment of diaper rash.

Administration of oxidative drugs with cytochrome P-450 inducers: Co-administration of p450 inducers (drugs that increase cytochrome p450 enzyme activity, such as via allosteric binding e.g. antihistamine or oral contraceptives, or coenzymes which include vitamin B complex or cofactors such as Na, Mg, Ca, Zn which play a role in optimizing enzyme activity) with oxidant drugs may increase the formation of toxic metabolites which oxidize Hb

Administration of oxidative drugs with base drugs that increase pH of intestine: Co-administration of base drugs that cause increased intestinal pH may promote the growth of gram negative organisms that convert nitrates to nitrites (in infants).

Dose related: A high dose of an oxidizing agent may produce methemoglobinemia if given in more than its recommended dose. Methylene blue may produce methemoglobinemia in large doses (it causes mHb formation up to about 7% of total Hb). The perinatal administration of higher doses of methylene blue (4 mg/kg) given amniotically has been reported to induce methemoglobinemia and hemolysis in non G6PD deficient infants, large doses (up to 15 mg/kg) may cause hemolysis; the total dosage should be not exceed 7mg/kg. Methylene blue should not be used for methemoglobinemia due either to chlorate poisoning or to the use of nitrites for cyanide poisoning.

Metoclopramide has induced methemoglobinemia in an infant after 1 mg/kg every six hours when given over a 36 hours period. Prilocaine in doses of 6-24 mg/kg (or greater) can induce methemoglobinemia, but local anesthetics may even produce methemoglobinemia after normal doses. The manufacturer estimates that isosorbide mononitrate in doses equivalent to 2 mg/kg would be required to generate methemoglobinemia of 10% or greater.

Duration of therapy: Chronic or intermittent administration of oxidative drugs may produce methemoglobinemia.

Examples: Metmemoglobinemia was reported in a female with pheochromocytoma who received Metoclopramide 20 mg three times daily for five months. Cotriamoxazol (trimethoprim / sulfamethoxazole) produced methemoglobinemia when given long term trimethoprim at a dose of 500mg. However, 100mg trimethoprim for four years not produce methemoglobinemia.

Route of administration: Articaine has not been associated with methemoglobinemia during dental anesthesia; however, it has occurred in some patients' who have undergone intravenous regional anesthesia.

Body surface area: When oxidative drugs have been applied to large area of the body this may produce methemoglobinemia more commonly than when applied just to small areas, and this is especially important when the application is to open skin, or to an infant. Clinical significant methemoglobinemia has developed in children treated with silver nitrate.

Age: Drugs are more likely to induce methemoglobinemia in children (particularly infants less than three months) due to their limited enzyme capacity at this earlier age. Therefore, Hb level should be monitored in infants whenever it is necessary to administer oxidative drugs. Infants and premature infants are particularly susceptible to the development of methemoglobinemia because their erythrocyte b5R activity is normally only 50 to 60% of the adult level of activity. Although cytochrome b5R levels rise to those of an adult within months of birth, young infants are unusually vulnerable to

developing toxic methemoglobinemia following exposure to a number of otherwise relatively harmless medications, local ointments, and dyes used on diapers.

The elderly have a high risk of developing methemoglobinemia after a normal therapeutic dose; for example, flutamide 250mg three times daily for two months produced methemoglobinemia in an elderly patient and methemoglobinemia has been reported in an elderly patient with CHF after receiving isosorbide dinitrate 60mg daily.

Disease: Patients with underlying cardiac, pulmonary, hematologic disease, liver cirrhosis, HIV infection or renal failure are more susceptible to development of the symptoms of methemoglobinemia. Patients with renal failure undergoing hemodialysis are more susceptible to development of methemoglobinemia, which has occurred with concentration of 21 mg/l of nitrate-nitrogen in the dialysis fluid. A water standard of 2 ppm of nitrate has been recommended for dialysis. In liver cirrhosis the red blood cells in those with cirrhosis are already under severe oxidative stress, especially in those where bleeding complications have arisen [5,10]. Almost all (94%) patients with methemoglobinemia were found to be anemic in a study by Ash-Bernal et al. [15].

Primaquine & dapsone alone, or in combination, produce methemoglobinemia in patients with HIV infection, and clinically significant methemoglobinemia, particularly when primaquine is given within 24 hours of the last dose of dapsone. Isosorbid dinitrate (in therapeutic doses) produced methemoglobinemia in patient with renal failure. Methemoglobin, from 28% to 70% has been reported in young burn patients with septicemia receiving silver nitrate treatment.

Hereditary: There are three types of hereditary methemoglobinemia. Two are inherited as autosomal recessive traits: cytochrome b5 reductase deficiency and cytochrome b5 deficiency. The third type is an autosomal dominant disorder, HbM disease in which there is a mutation in the globin molecule. Patients with mHb reductase deficiency or abnormal Hb (hemoglobin "m") develop methemoglobinemia after exposed to oxidizing drugs as well as in overdose.

Patients with a genetic deficiency are generally asymptomatic and the condition may not have clinical significance until the patient is exposed to an oxidizing drug or to chemicals in doses which have no effect in normal people. Chloroquine has produced methemoglobinemia in oral doses of 30-300mg, chloroquine as well as other anti-malarial may provoke methemoglobinemia in enzyme deficient subjects in doses that no effect on normal people.

Patients with G6PD deficiency can develop methemoglobinemia following administration of methylene blue. Rasburicase is contraindicated in G6PD deficient patients due to the risk of acute hemolytic anemia (AHA) and possibly methemoglobinemia. Therefore, rasburicase is contraindicated in patients with known G6PD deficiency and the manufacturer recommends screening all patients with high risk for G6PD deficiency before initiating rasburicase therapy [16].

Diet status: High levels of nitrate and nitrites in some vegetables (e.g. carrot, beetroot, radish juices) have been reported, depending upon factors such as fertilizer use, method of storage, bacterial contamination, and method of preparing (e.g. removal of stems, peeling, blanching). Although the adverse health effects of dietary nitrate and nitrite are uncertain, consumption of homemade and small scale industrially produced raw vegetable juices (e.g. use of beetroot juice to improve athletic performance) may lead to unacceptably high levels of nitrite intake, increased nitric oxide production, and possibly increased risk of methemoglobinemia [17].

Foods high in nitrate preservatives (especially in meats) may induce methemoglobinemia in infants and in persons with hereditary NADH dependent methemoglobin reductase deficiency whereas foods high in nitrite preservatives (especially in meats) may induce methemoglobinemia in both normal persons and in persons with hereditary NADH dependent methemoglobin reductase deficiency. For example, methemoglobinemia developed in five members of a household in New York in 2002 after eating a meal seasoned with a white crystalline substance from a plastic bag labeled “refined iodized table salt" in Arabic and English (sea salt contain 100% of sodium nitrite). In addition, ingestion of vegetables with high nitrate content (e.g. carrots, spinach, cabbage, beets) can cause methemoglobinemia and should be avoided in infants less than four months old.

Water: Well water with high nitrogen content, especially in rural (agricultural) may induce methemoglobinemia in infants who are fed formula and other infant foods prepared with contaminated well water.

Drinking water: The US federal maximum contaminant level of nitrate in drinking water is 45 ppm for nitrate or 10 ppm for nitrate - nitrogen methemoglobinemia has been developed in infants who have ingested municipal water containing 13.3 to 24.4 ppm of nitrate–nitrogen.

Gender: There is no gender predisposition [15].

Weight: An association between methemoglobinemia and weight in the lower percentiles has been reported [18].

Recommendations for the Prevention of Methemoglobinemia

Supplemental antioxidants such as ascorbic acid (vitamin C), *N*-acetyl cysteine and tocopherol (vitamin E) have been used as adjuvants or alternatives to methylene blue with no confirmed benefit. Exchange transfusion may have a role in the management of severe hemolysis or in G6PD deficiency associated with life-threatening methaemoglobinaemia. Here are some recommendations as:

Co-administration of antioxidant drugs (e.g. ascorbic acid) with drugs that undergo entro hepatic circulation. This may prevent the oxidization of Hb when given together in recommended dose whole over treatment. Ascorbic acid not recommended in acute acquired metbemoglobinemia [19].

Antidote N-acetyl cysteine act both as precursor for glutathione synthesis and as an electron donor, therefore, reducing the toxic metabolites and/or modifying the inflammation induced by oxidation.

Administration of oxidant drug with cytochrome p450 inhibitors to prevent the formation of toxic metabolites

Avoid administration of oxidant drugs with cytochrome p450 inducers.

Conclusion

Drugs rarely produce methemoglobinemia when given in recommended doses to normal people. However, acquired methemoglobinemia appears to be relatively common in infants within three months, and also in patients with congenital deficiencies

following exposure to oxidative drugs. The risk of methemoglobinemia increased in infants and in the elderly if they have underlying health problems (cardiac, renal, pulmonary, or hematologic) or by concurrent use more than one oxidant drug, high dose, or chronic or intermittent administration of therapeutic doses. Monitoring of mHb levels suggested in patients with a high risk of methemoglobinemia

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