

Drugs may be 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 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. 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 methemoglobin 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 oxidants 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 oxidants agents. Observation of asymptomatic individuals for 24 hours may be advisable with exposure to some oxidants drugs which require biochemical transformation before causing Methemoglobinemia.

Keywords: Antimalarials; Methemoglobinemia; Anesthetics

Introduction

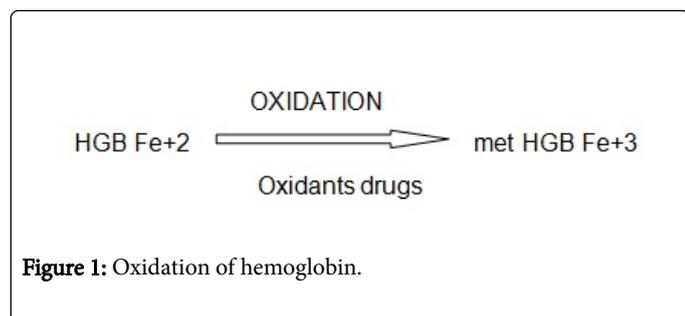
Methemoglobinemia is a rare disorder of the blood in which there is an increase in the proportion of hemoglobin present in the oxidized form (methemoglobin). It may be congenital, due either to a deficiency of methemoglobin reductase or to a structural abnormality of hemoglobin, or it may be acquired, 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 methemoglobin 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 oxidants 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 oxidants 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].

Pharmacology

Mechanism of action

In normal persons, the methemoglobin (met Hgb) levels are kept below 1% by a 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 glutathione and glucose-6-phosphate dehydrogenase). 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.



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 a potent inducer of methemoglobinemia and hemolysis, but it converted first to phenylhydroxyamine that is oxidized to nitrosobenzene by Hgb (Fe(II)) and oxygen. The nitrosobenzene is subsequently reduced by a NADPH flavin reductase back to aniline, using NADPH derived from glucose-6-phosphate dehydrogenase and the hexose monophosphate shunt. Alternatively glutathione can be used as a source of reducing power. Aniline and nitroso-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

methemoglobin and consuming glutathione compared to the sulfamethoxazole hydroxylamine 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 individuals, and rate of absorption or enterohepatic 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 methemoglobinemia. 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 [3,5].

Drugs may 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. 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 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. (Table 1 summarizes the drugs that induce methemoglobinemia) [3,5,6-9].

Medical Group	Drugs
Analgesic and Antipyretics	Acetaminophen-Phenacetin-Antipyrin (Antipyrin and Benzocaine) Auralgan® Opiate Agonists: Fentanyl Urinary Tract Analgesic: Phenazopyridine Celecoxib
Anticonvulsants	Phenobarbital, Phenytoin, Sodium Valproate
Anti-Infective Drugs	
Antimicrobials	Sulfonamide: Cotrimoxazole (Sulfamethoxazole-Trimethoprim)-Sulfanilamide-Sulfapyridine-Sulfathiazole
	Sulfon: Dapsone Nitrofurantoin Clofazimine
	Phenazopyridine hydrochloride
Antimalarial	Chloroquine-Primaquine Phosphate-Quinine
Antituberculosis	Para-Aminosalicylic Acid-Rifampin
Hormones	Flutamide
Psychotherapeutic	Phenelzine; Piperazine; Trazodone
Vasodilator	
Nitrate derivative	Nitroglycerin; Isosorbide Dinitrate; Silver Nitrate; Sodium Nitrate; Nitrate Salt; Erythryl Tetranitrate
Nitrites Derivative	Amyl Nitrite; Bismuth Subnitrite; Sodium Nitroprusside; Sodium Nitrite; Nitric Oxide

Vitamines	Menadione (Vitamine K3)
Miscellaneous	
Topical Anaesthetic	Benzocaine; Lidocaine hydrochloride; Prilocaine hydrochloride
Local Anaesthetics	Amethocain; Articaïne; Benzocain; Cetacaine; Lidocaine; Prilocaine; Procaine; Bupivacaine Hydrochloride
Anti-Infective Topical	Carbol-Fuchsin Topical Solution (Phenol; Resorcinol; Basic Fuchsin (Rosanilind And Pararosaniline Hydrochlorides) Cetrimide; Triclocarbon Soap (TCC)
Other Topical	Hydroquinone; Potassium Permanganate
Other	Methylene Blue; Metoclopramide Hydrochloride; Riluzole; Rasburicase

Table 1: Drugs that induce Methemoglobinemia.

Oxidizing agents accelerate 100 to a 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 Table 2 summarizes the chemical that may induce methemoglobinemia [3-6].

Acetanilide	Chromates	Nitrates	Naphthalene
Alloxan	Dimethyl sulfoxide	Potassium nitrate*	Nitrophenol
Anilines	Dinitrophenol	Sodium nitrate	Nitrobenzene
Aminophenol	Phenol	Nitrites	Nitroethane
Arsine	Fumes	Isobutyl nitrite	Paraquat
Benzene derivatives	Automobile exhaust	Butyl nitrite	Toluidine
Bivalent copper	fumes		Trinitrotoluene (TNT)
Chlorates	Burning wood and plastic		

Table 2: Chemical agents capable of inducing Methemoglobinemia.

Predisposing Factors

Drugs induced methemoglobinemia depend on many factors such as:

Potency of Oxidizing Agent, strong oxidizing drugs produce methemoglobinemia more than weak oxidizing drugs (Table 3). Drugs containing aniline group, nitroso group or which metabolized 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 over dose. Although Acetaminophen active metabolite of Phenacetin, acetaminophen does not cause methemoglobin formation because of the absence of nitroso metabolites. But methemoglobinemia has been reported in one patient after Acetaminophen dose but unconfirmed by other finding. Phenazopyridine, *in vivo* 50% of phenazopyridine is metabolized to aniline. Phenazopyridine induces methemoglobinemia after therapeutic use and over dose (aniline produced by 200 mg of

phenazopyridine three times a day exceeds the 35 mg maximal allowable dose of aniline).

Medical Group	Rarely	Uncommon	Common
Analgesic-Antipyretics	Acetaminophen		Phenazopyridine
	Fentanyl		Phenacetin
Anticonvulsants	Phenobarbital		
Anti-Infectives Agents	Chloroquine	Sulfonamides	Dapsone
	Nitrofurantoin		Primaquine
Local or Topical Anaesthetics	Lidocaine	Amethocaine	Benzocain (Topical)
		Cetacaine	Prilocaine
		Tetracaine	
Vasodilators Agents		Nitrates derivatives	Nitrites Derivatives
Miscellaneous		Methylene Blue	
		Metoclopramide	

Table 3: Incidence of most drugs that cause Methemoglobinemia.

Nitrate Derivatives, which are relatively nontoxic, can be reduced to Nitrites Derivatives (more potent methemoglobin-inducing agents) in the gut by bacteria such as *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Aerobacter cloacae*, *Escherichia spp.*, and *Salmonella*. The world health organization limit for daily intake of Nitrate is 5 mg/kg, and Nitrite 0.4 mg/kg. Local Injection or Topical Administration of Anaesthetics induce methemoglobinemia, and Prilocaine is more commonly induce methemoglobinemia more than other local anaesthetics, the effect is due to metabolism prilocaine to an aniline like structure and to o-toluidine, both known methemoglobin inducers. The author, from the University of Montreal, reviews 242 published episodes of local anesthetic-related methemoglobinemia and presents 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 the cases involved a procedure done outside of the operating room and 6% involved an over-the-counter medication. In retrospective series of 138 cases at 2 teaching hospitals, the authors found Dapsone was the most common etiology of acquired methemoglobinemia, accounting for 42% of all cases [7].

Concomitant Administration more than One Oxidant Drugs

Coadminister more than one of oxidant drugs especial when both drugs are strong oxidant drugs may increase formation of toxic metabolites or enhance oxidize Hg if the drugs not require biochemical transformation. **Examples:** Administration Primaquine to patient with HIV infection within 24 hours of last dose of Dapsone can produce clinically significant methemoglobinemia. Emla Cream (Prilocaine-Lidocaine) or Aurlgan (Antipyrin and Benzocain induce methemoglobinemia in infant less than 3 months application. Methemoglobin level increased when isosorbide dinitrate and nitroglycerin ointment were given in combination. Benzocaine-containing over the counter products with miconazole nitrate vaginal suppositories induced clinical significant methemoglobinemia in female.

Methemoglobinemia has been reported developed in infant after 36 hours of administration a topical anesthetic cream containing 5% benzocaine and 2% resorcinol for treatment diaper rash. And Concomitant Administration Oxidant Drug With Cytochrome P-450 Inducers Co-administration of p-450 inducers (drugs that increased cytochrome p-450 enzyme activity such as (drugs can enhance enzyme activity by allosteric binding e.g. antihistamine or oral contraceptives/or coenzyme include vitamins b complex or cofactors such as Na, Mg, Ca, Zn which play role in optimizing enzyme activity) with oxidant drugs may increase the formation of toxic metabolites which oxidize hemoglobin. or concomitant administration of oxidant drug with base drugs that increase PH of intestinal: Coadminister base drugs lead to increase intestinal PH may promote the growth of gram negative organisms that convert nitrates to nitrites (in infant).

Dose related: High dose of oxidizing agent may produce methemoglobinemia more than recommended dose. Methylene Blue may produce methemoglobinemia in large dose (it cause methemoglobin formation up to about 7% of total hemoglobin). 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 dose up to 15 mg/kg may cause hemolysis; the total dosage should be not exceed 7 mg/kg. Methylene blue should not be used for methemoglobinemia due either to chlorate poisoning or to the use of nitrites for cyanide poisoning since increased toxicity may result. Metoclopramide induced methemoglobinemia in infant after 1 mg/kg every six hours for 36 hours period. Prilocaine in dose 6-24 mg/kg or greater induces methemoglobinemia, but local anaesthetics may be produce methemoglobinemia after usual doses. The manufacturer estimates that Isosorbide Mononitrate doses equivalent to 2 mg/kg would be required to generate 10% or greater methemoglobinemia.

Duration of therapy: Chronic or intermittent administration of oxidant drugs may produce methemoglobinemia. **Examples:** methemoglobinemia reported in female with pheochromocytoma who received Metoclopramide 20 mg three times daily for five months. Cotriamoxazol (trimethoprim/sulfamethoxazole) produced methemoglobinemia in dose 500 mg of trimethoprim for long term; 100 mg of trimethoprim for four years not produce methemoglobinemia.

Route of administration: Articaine, do not reported methemoglobinemia during dental anesthesia, whoever reported in some patients undergoing intravenous regional anesthesia.

Body surface area: When oxidant drug apply to large area of the body, may produce methemoglobinemia more than small area especial when application to open skin, or to infant. Clinical significant methemoglobinemia developed in children treated with Silver Nitrate.

Age: The drugs more susceptible to induce methemoglobinemia in children particularly infants less than three months due to their limited enzyme capacity. So that should be monitor hemoglobin level in infant when necessary administered oxidant drugs. Infants and premature infants are particularly susceptible to the development of methemoglobinemia because their erythrocyte b5R activity is normally 50 to 60 percent of adult 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 Elderly high risk to develop methemoglobinemia after therapeutic dose e.g. Flutamide 250 mg three times daily for two months produced methemoglobinemia in elderly patient. Methemoglobinemia reported in elderly patient with CHF after received Isosorbide Dinitrate 60 mg daily.

Disease: Patients with underlying cardiac, pulmonary, hematologic disease, liver cirrhosis, HIV infection or renal failure are more susceptible to development of symptoms 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. At 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. [3,5], Almost all (94%) patients with methemoglobinemia were anemic in Bernal and et al study [6,7]. Primaquine and Dapsone alone or in combination with together produce methemoglobinemia in patient with HIV infection, clinically significant methemoglobinemia, particularly when primaquine is given within 24 hours of last dose of dapsone. Isosorbide Dinitrate (in therapeutic dose) 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, hemoglobin M (Hb M) disease in which there is a mutation in the globin molecule. Patients with methemoglobin reductase deficiency or abnormal hemoglobin's (hemoglobin "m") develop methemoglobinemia offer exposed to an oxidizing drug as well as in over dose. Patients with a genetic deficiency generally asymptomatic and the condition may not have clinical significance until the patient is exposed to an oxidizing drug or chemical in doses which have no effect in normal persons.

Chloroquine, produced methemoglobinemia in doses 30-300 mg orally, chloroquineas well as other antimalarial may provoke methemoglobinemia in enzyme-deficient subjects in doses that no effect on normal persons. Patients with glucose 6 phosphate dehydrogenase (G-6-PD) deficiency can develop methemoglobinemia following methylene blue administration.

Rasburicase [8,9] 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 [10].

Nutrition or diet status: High levels of nitrate and nitrites in some vegetables (eg: carrot, beetroot, radish juices) have been reported, depending upon factors such as fertilizer use, method of storage, bacterial contamination, and method of preparing (eg: removal of stems, peeling, blanching). Although the adverse health effects of dietary nitrate and nitrite are uncertain, consumption of home-made and small-scale industrially produced raw vegetable juices (eg: 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 [11,12]. 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.

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 infant's ingestion municipal water containing 13.3 to 24.4 ppm of nitrate-nitrogen.

Gender: There was no gender predisposition [7].

Weight: An association between methemoglobinemia and weight in the lower percentiles has been reported [11].

Recommendation for prevention of Methemoglobinemia

Supplemental antioxidants such as ascorbic acid (vitamin C), N-acetylcysteine 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 haemolysis or in G-6-P-D deficiency associated with life-threatening methaemoglobinemia where methylene blue is relatively contraindicated. There are some recommendations as:

- Co-administer antioxidants drug (ascorbic acid) with drugs which undergo enterohepatic circulation (oxidant drugs that undergo enterohepatic circulation produce prolonged methemoglobinemia not due to regenerates oxidant drugs such as dapson) may prevent oxidize hemoglobin, when given with together in recommended dose whole over treatment but ascorbic acid not recommended in acute acquired methemoglobinemia.
- Antidote N-acetylcysteine act both as precursor to glutathione synthesis and as an electron donor, directly reducing the toxic metabolites or modifying the inflammation induced by oxidation.
- Given N-acetylcysteine orally weekly
- Concurrent Administration of oxidant drug with cytochrome p-450 inhibitors to prevent the formation of toxic metabolites.
- Avoidance administration of oxidant drugs with cytochrome p-450 inducers

- Co-administration oxidant drugs with enzyme inducers may increase the formation of toxic metabolites.
- Concomitant administration of oxidant drugs with drugs which metabolize by cytochrome p-450 selection of the drugs that metabolized by cytochrome p-450 (depend on state of the patient and disease) to given with oxidant drugs to decrease capacity of cytochrome system p-450 to metabolized drugs to toxic metabolites advisable the patient to avoid eating foods high in nitrite preservative or vegetables which high in nitrate contents (especial infants)

Conclusion

Drugs rarely produce methemoglobinemia when given in recommended dose to normal persons but acquired methemoglobinemia appears to be relatively common in infants within three months and patients with congenital deficiencies following exposed to oxidants drugs. The risk of methemoglobinemia increased in infants, elderly, Persons with underlying health problems (Cardic, renal pulmonologic of hematologic) or by concurrent use more than one oxidant drugs, high dose, chronic or intermittent administration of therapeutic doses. Monitoring of methemoglobin levels suggested in patient with high risk of methemoglobinemia.

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