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Methemoglobinemia and Medications A to Z

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A patient with celiac disease complains about fatigue and being out of shape. He looks pale. You learn he recently increased his dapsone dose because his dermatitis herpetiformis has flared up. What might be going on?

Recent warnings from Health Canada have highlighted the risk of methemoglobinemia with benzocaine,[1] but this rare and potentially serious adverse effect can occur with a number of other medications.

What is methemoglobin?
Methemoglobin (MeHb) is hemoglobin (Hb) containing oxidized (rather than oxygenated) iron. Normal hemoglobin contains four iron atoms in the ferrous (Fe^{+2}) state. Oxygen binds to the ferrous ions and is transported to tissues where it is released in response to a lower oxygen gradient. If the ferrous ion loses an electron to another drug or chemical and is oxidized to the ferric (Fe^{+3}) state, it can no longer bind oxygen. As well, if even one of the iron atoms becomes oxidized the release of bound oxygen from the other iron atoms in the haemoglobin molecule is impaired. So methemoglobin reduces oxygen carrying capacity and reduces oxygen release to tissues. Carbon dioxide transport from the tissues to the lungs for elimination is also impaired.[2-5]

Methemoglobin levels are usually expressed as a percentage of total hemoglobin. A small amount of hemoglobin naturally becomes oxidized during oxygen transport, but endogenous mechanisms exist to reduce MeHb, so normally only ~1-2% of the body's hemoglobin exists as MeHb.[2-5]

Endogenous reduction of MeHb back to normal Hb in the red blood cell is catalysed primarily

via cytochrome b5 MeHb reductase. This enzyme is less active in infants less than 6 months, making them more susceptible to developing methemoglobinemia than adults. Some individuals are also more susceptible or always have elevated levels of MeHb due to an inability to synthesize adequate amounts of cytochrome b5 MeHb reductase or because their hemoglobin is abnormal (e.g. hemoglobin M).[2-6]

Another reduction pathway is the reduced nicotine adenine dinucleotide phosphate (NADPH)-dependent MeHb reductase, which normally reduces a negligible amount of MeHb. However, this pathway is key to antidotal treatment. Non-enzymatic reduction also occurs (albeit very slowly) with the help of antioxidants such as glutathione and ascorbic acid.[2-5]

Clinical Effects

If the endogenous MeHb reducing systems are overwhelmed and the proportion of MeHb becomes high enough, symptoms of hypoxia occur. Signs and symptoms correlate with MeHb levels (Table 1). Anemia can worsen symptoms since the patient's overall oxygen carrying capacity is further reduced. Patients with conditions such as ischemic heart disease or pulmonary disease may have more severe symptoms or develop symptoms at lower MeHb levels.[2-4]

Table 1: Signs and symptoms associated with elevated MeHb levels.[2-4]

MetHb concentration (%)	**Signs and symptoms**
0-3% (normal)	None
3-10%	Blue-grey skin appearance (cyanosis), may be asymptomatic
10-20%	Cyanosis, chocolate brown colour of blood
20-50%	Mental changes (headache, fatigue, anxiety, confusion, dizziness), syncope, tachycardia, dyspnea and tachypnea, weakness, exercise tolerance
50-70%	Metabolic acidosis, seizures, coma, dysrhythmias
>70%	Potentially lethal

Causes

A variety of naturally occurring substances including nitrates in vegetables (e.g. Swiss chard, beans, zucchini); environmental and industrial chemicals (e.g. nitrates in well water, engine exhaust, aniline, naphthalene); and therapeutic agents are capable of causing MeHb formation, either directly or indirectly through their metabolites.[2-4,7] Medications reported to cause MeHb are listed in Table 2.

Table 2: Some medications reported to cause methemoglobinemia

		Notes
A	Acetaminophen[8-12]	Acetaminophen rarely causes MeHb in humans at therapeutic doses, but it can in overdoses or in combination with other MeHb inducers. MeHb is a common finding of acetaminophen toxicity in cats and dogs.
	Atovaquone[13]	MeHb is mentioned as an adverse effect of Mepron® (product monograph).
B	Benzocaine[14-17]	Benzocaine is one of the most common causes of significant MeHb. Most of the serious cases involve use of topical sprays used in anesthesia. While the majority of children who accidental ingest teething gels remain asymptomatic, life-threatening MeHb (~70%) has occurred.
	Buprenorphine-naloxone[13]	MeHb is mentioned as an adverse effect of Suboxone® (product monograph).
C	Celecoxib[18] Cloroquine[19] Cotrimoxazole[20,21] Cyclophosphamide[3]	Celecoxib 100 mg BID resulted in MeHb of 9% and confusion in one patient. Cotrimoxazole has caused MeHb on its own and when given with other MeHb inducers.
D	Dapsone[2]	Dapsone is another frequently cited cause of MeHb. Because of the long half-life of dapsone and its hydroxylamine metabolite, prolonged or repeated antidote treatment or exchange transfusion may be required.
	Disulfiram[22]	Disulfiram was suspected to cause MeHb of 53% in one fatality. The metabolite diethylthiocarbamate can produce MeHb in vitro.
E	EMLA (lidocaine-prilocaine)[23]	Application of a large amount of EMLA for laser hair removal resulted in symptomatic elevated MeHb (20%) requiring treatment.
F	Flutamide[24,25]	MeHb is mentioned as a possible side effect in the product monograph and is usually mild. Sulfhemoglobinemia has occurred that is mistaken for MeHb but does not respond to methylene blue.
H	Hydrogen peroxide[26-28]	Hydrogen peroxide disinfection of dialysis machines has been linked to MeHb. Topical application of hydrogen peroxide to mucous membranes caused MeHb in a patient deficient of the enzyme catalase. See rasburicase.

I	Ibuprofen[29]	Cyanosis with MeHb levels of 27.2% occurred in a 7-month-old infant, eight hours after a dose of ibuprofen 7.5 mg/kg. Other causes were ruled out.
	Ifosfamide[30]	Marked MeHb (~50%) occurred in a patient receiving ifosfamide who was also taking phenobarbital for seizures. Enzyme induction with increased formation of MeHb inducing metabolites was suspected to be involved.
	Interactions[12,21,31]	Oxidative stress may be additive when more than one potential MeHb inducers are used together (e.g. sulfonamides and prilocaine; nitric oxide and cotrimoxazole; acetaminophen and sodium nitrate).
L	Lidocaine[16] (and other local anesthetics)	Lidocaine appears to be much less likely to cause MeHb compared to benzocaine, considering the frequency of lidocaine use.
M	Metoclopramide[32,33]	Metoclopramide has occasionally been reported to cause MeHb in neonates and less frequently in adults, although significant MeHb (>40%) has been reported.
N	Nitrites and nitrates (amyl nitrite, silver nitrate, nitroglycerin, nitroprusside)[34-36]	Environmental and industrial nitrites and nitrates are common inducers of MeHb; therapeutic nitrates can cause MeHb as well.
	Nitric Oxide	Therapeutic inhaled nitric oxide at less than 40 ppm usually causes only a mild elevation in MeHb.
P	Phenazopyridine[2,37,38]	Phenazopyridine is another common cause of MeHb in both children and adults. The resemblance to candy and sugar coating makes phenazopyridine tablets attractive to children.
	Prilocaine[16]	Prilocaine is the next most common local anesthetic reported to cause MeHb (after benzocaine).
	Primaquine[39]	Primaquine causes a usually mild MeHb when used as an antimalarial but MeHb levels >30% can be seen occasionally.
R	Rasburicase[40]	Rasburicase (recombinant urate oxidase) catalyses the conversion of urate to allantoin, producing hydrogen peroxide in the process which may contribute to development of MeHb.
	Riluzole[41,42]	MeHb levels of 12 to 18% have been seen following overdoses of riluzole.
S	Sulfonamides (sulfadiazine, sulphanilamide, sulfapyridine, sulfasalazine)[43-45]	Topical silver sulfadiazine burn dressings caused MeHb in a young boy with thalassemia. Sulfanilamide is not available for human use in Canada anymore. The sulfapyridine portion is responsible for MeHb seen with sulfasalazine.
T	Tetracaine[46]	Self-medication with tetracaine lozenges caused MeHb in one case. Tetracaine by itself appears to have a low propensity to cause MeHb.

V	Vitamin K (menadione)[3,47]	Menadione is approved only for veterinary use in Canada.
Z	Zopiclone[48,49]	MeHb levels ranging from 10.4% to 23.8% have been reported in patients following large overdoses of zopiclone.

MeHb = methemoglobin or methemoglobinemia

Treatment

The mainstay of treatment is discontinuation of the offending agent, which is sufficient for many patients with mild methemoglobinemia. If a patient is symptomatic or has a MeHb level greater than 20-25%, supportive measures like supplemental oxygen and antidote treatment with methylene blue may be necessary.[2,3,14]

Methylene blue is reduced by the NADPH-dependent MeHb reductase enzyme system to leukomethylene blue, which in turn is able to directly reduce MeHb to Hb. An intravenous dose of 1-2 mg/kg usually results in rapid reduction in MeHb levels and improvement in symptoms.[2,14] Repeated doses may be required in some cases, but caution is required as high cumulative doses of methylene blue can actually exacerbate MeHb or cause hemolysis. In addition, since NADPH generation is dependent on glucose-6-phosphate dehydrogenase (G6PD), methylene blue may not work in some patients with severe G6PD deficiency and can cause hemolysis.[2,14] Vitamin C and glutathione replacement are not useful for reversal of acute methemoglobinemia.[2]

Summary

Methemoglobinemia is an uncommon but potentially life-threatening condition that can be caused by a variety of drugs at therapeutic or supratherapeutic doses. Avoidance or judicious use of high-risk drugs, having a high index of suspicion in high-risk patients, prompt discontinuation of offending agents, supportive care and treatment with methylene blue will reduce morbidity.

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