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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 dapsons 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 nicotinic 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 intolerance
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 accidentally 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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References:

1. Health Canada Health Canada reminds Canadians of health risks associated with topical benzocaine products. April 19, 2011. Available from URL: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2011/2011_59-eng.php. Accessed 05/2011.
2. Goldfrank's Toxicologic emergencies, 9th ed (2010), p. 1698-1710.
3. Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management *Ann Emerg Med*. 1999; 34: 646-56.
4. Trapp L, Will J. Acquired methemoglobinemia revisited. *Dent Clin N Am*. 2010; 54: 665-75.
5. Casarett & Doull's toxicology: the basic science of poisons. 7th ed (2008), p. 460-2.
6. Percy MJ, McFerran NV, Lappin TR. Disorders of oxidised haemoglobin. *Blood Rev*. 2005; 19: 61-8.
7. Bradberry SM. Occupational methaemoglobinaemia. Mechanisms of production, features, diagnosis and management including the use of methylene blue. *Toxicol Rev*. 2003; 22: 13-27.
8. Maclean D, Robertson PG, Bain S. Methaemoglobinaemia and paracetamol. *Br Med J*. 1968; 9: 390.
9. Nash SL, Oehme FW. A review of acetaminophen's effect on methemoglobin, glutathione, and some related enzymes. *Vet Hum Toxicol*. 1984; 26: 123-32.
10. Golden DP, Mosby EL, Smith D, et al. Acetaminophen toxicity. Report of two cases. *Oral Surg Oral Med Oral Pathol*. 1981; 51: 385-390.
11. Dunn RJ. Massive sulfasalazine and paracetamol ingestion causing acidosis, hyperglycemia, coagulopathy, and methemoglobinemia. *J Toxicol Clin Toxicol*. 1998; 36: 239-42.
12. Kobayashi T, Kawabata M, Tanaka S, et al. Methemoglobinemia induced by combined use of sodium nitrate and acetaminophen. *Intern Med*. 2000; 39: 860.
13. eCPS (online via e-Therapeutics) - various monographs.
14. Kent DA. Poison Management Manual, 5th ed. Vancouver: BC Drug and Poison Information Centre (in press).
15. Spiller HA, Revolinski DH, Winter ML, et al. Multi-center retrospective evaluation of oral benzocaine exposure in children. *Vet Hum Toxicol*. 2000; 42: 228-31.
16. Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. *Anesth Analg*. 2009; 108: 837-45.
17. Chung NY, Cho JH, Lee IH, et al. Severe methemoglobinemia linked to gel-type topical benzocaine use: a case report. *J Emerg Med*. 2010; 38: 601-6.
18. Kaushik P, Zuckerman SJ, Campo NJ, et al. Celecoxib-induced methemoglobinemia. *Ann Pharmacother*. 2004; 38: 1635-8.
19. Sharma N, Varma S. Unusual life-threatening adverse drug effects with chloroquine in a young girl. *J Postgrad Med*. 2003; 49: 187.
20. Koirala J. Trimethoprim-sulfamethoxazole-induced methemoglobinemia in an HIV-infected patient. *Mayo Clin Proc*. 2004; 829-30.
21. Lopez A, Bernardo B, López-Herce J, et al. Methaemoglobinaemia secondary to treatment with trimethoprim and sulphamethoxazole associated with inhaled nitric oxide. *Acta Paediatr*. 1999; 88: 915-6.
22. Stransky G, Lambing MK, Simmons GT, et al. Methemoglobinemia in a fatal case of disulfiram-ethanol reaction. *J Anal Toxicol*. 1997; 21: 178-9.
23. Hahn IH, Hoffman RS, Nelson LS. EMLA-induced methemoglobinemia and systemic topical anesthetic toxicity. *J Emerg Med*. 2004; 26: 85-8.
24. Kahn AM, Singh NT, Bilgrami S. Flutamide induced methemoglobinemia. *J Urol*. 1997; 157: 1363.
25. Kouides PA, Abboud CN, Fairbanks VF. Flutamide-induced cyanosis refractory to methylene blue therapy. *Br J Haematol*. 1996; 94: 73-5.
26. Bek MJ, Laule S, Reichert-Junger C, et al. Methemoglobinemia in critically ill patients during extended hemodialysis and simultaneous disinfection of the hospital water supply. *Crit Care*. 2009; 13: R162.
27. Hamada Y, Kameyama Y, Iizuka T, et al. Methemoglobinemia from hydrogen peroxide in a patient with acatalasemia. *Anesthesiology*. 2004; 101: 247-8.
28. Davidovits M, Barak A, Cleper R, et al. Methaemoglobinaemia and haemolysis associated with hydrogen peroxide in a paediatric haemodialysis centre: a warning note. *Nephrol Dial Transplant*. 2003; 18: 2354-8.
29. Khemiri M, Labassi A Jr, Bagais A Jr, et al. Toxic methemoglobinemia due to ibuprofen: report of a pediatric case. *J Emerg Med*. 2010; 39: 216-7.
30. Hadjiliadis D, Govert JA. Methemoglobinemia after infusion of ifosfamide chemotherapy: first report of a potentially serious adverse reaction related to ifosfamide. *Chest*. 2000; 118: 1208-10.
31. Naquib M, Magboul MM, Samarkandi AH, et al. Adverse effects and drug interactions associated with local and regional anaesthesia. *Drug Safety*. 1998; 18: 221-50.
32. Mary AM, Bhupalam L. Metoclopramide-induced methemoglobinemia in an adult. *J Ky Med Assoc*. 2000; 98: 245-7. [Medline abstract].
33. Karadsheh NS, Shaker Q, Ratroat B. Metoclopramide-induced methemoglobinemia in a patient with co-existing deficiency of glucose-6-phosphate dehydrogenase and NADH-cytochrome b5 reductase: failure of methylene blue treatment. *Haematologica*. 2001; 86: 659-60.
34. Chou TD, Gibran NS, Urdahl K, et al. Methemoglobinemia secondary to topical silver nitrate therapy--a case report. *Burns*. 1999; 25: 549-52.
35. Hovenga S, Koenders ME, van der Werf TS, et al. Methaemoglobinaemia after inhalation of nitric oxide for treatment of hydrochlorothiazide-induced pulmonary oedema. *Lancet*. 1996; 348: 1035-6.
36. Nakajima W, Ishida A, Arai H, et al. Methaemoglobinaemia after inhalation of nitric oxide in infant with pulmonary hypertension. *Lancet*. 1997; 350: 1002-3.
37. Gold NA, Bithoney WG. Methemoglobinemia due to ingestion of at most three pills of pyridium in a 2-year-old: case report and review. *J Emerg Med*. 2003; 25: 143-8.
38. Christensen CM, Farrar HC, Kearns GL. Protracted methemoglobinemia after phenazopyridine overdose in an infant. *J Clin Pharmacol*. 1996; 36: 112-6.
39. Carmon-Fonseca J, Alvarez G, Maestre A. Methemoglobinemia and adverse events in Plasmodium vivax malaria patients associated with high doses of primaquine treatment. *Am J Trop Med Hyg*. 2009; 80: 188-93.
40. Kizer N, Martinez E, Powell M. Report of two cases of rasburicase-induced methemoglobinemia. *Leuk Lymphoma*. 2006; 47: 2648-50.
41. Woolf A, Carstairs SD, Tanen DA. Riluzole-induced methemoglobinemia. *Ann Emerg Med*. 2004; 43: 294.
42. Viallon A, Page Y, Bertrand JC. Methemoglobinemia due to riluzole. *NEJM*. 2000; 343: 665-6.
43. Bristol I, Brown J, Slomovitz BM, et al. Methemoglobinemia induced by topical vaginal sulfanilamide cream in a patient with cervical cancer: a case report. *Gynecol Oncol*. 2005; 97: 953-6.
44. Tsai T-C, Peng SK, Shih YR, et al. Sulfadiazine-induced methemoglobinemia in a boy with thalassemia. *Can J Anaesth*. 2005; 52: 1002-3.

45. Pirmohamed M, Coleman MD, Hussain F, et al. Direct and metabolism-dependent toxicity of sulphasalazine and its principal metabolites towards human erythrocytes and leucocytes. *Br J Clin Pharmacol*. 1991; 32: 303-10.
46. Lavergne S, Darmon M, Levy V, et al. Methemoglobinemia and acute hemolysis after tetracaine lozenge use. *J Crit Care*. 2006; 21: 112-4.
47. Schalm's veterinary haematology. 5th ed. (2000), p. 181. (Available on-line through Google books). Accessed 05/2011.
48. Kung SW, Tse ML, Chan YC, et al. Zopiclone-associated methemoglobinemia and renal impairment. *Clin Toxicol*. 2008; 46: 1099-100.
49. Fung HT, Lai CH, Wong OF, et al. Two cases of methemoglobinemia following zopiclone ingestion. *Clin Toxicol*. 2008; 46: 167-70.

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